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THE TREATMENT OF ACQUIRED HEMOLYTIC ANEMIA WITH ADRENOCORTICOTROPHIC HORMONE (ACTH)*

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ACQUIRED hemolytic anemia, in contrast with the hereditary types, is usually due to an "extrinsic" mechanism acting upon normal red blood cells, injuring them and leading to an increased rate of destruction. In many cases, a fundamental pathologic process such as lymphosarcoma or leukemia can be found (symptomatic[1-3] or secondary types), but most of the cases have no well defined etiology — that is, they are "idiopathic." Whether the anemia is symptomatic or idiopathic, an abnormal antibody can usually be found free in the blood or adsorbed to the red-cell surface. We have postulated that this antibody, which is ordinarily more active against the patient's own red cells (autoantibody) than against those of other persons (isoantibody), is the most important single factor in causing red-cell injury and thus the hemolytic state.[4] The mechanism by which the body develops autosensitization and thus autohemolysis, is by no means clear, but it is probable that antibody is produced either by the reticuloendothelial system[5] or by the system of lymphocytes.[6, 7] Modification and even suppression of antibody production can at times be achieved by splenectomy,[8] but in many cases this operation results in little if any effect. For this reason, we have attempted for some years to modify antibody production by various means, including x-ray therapy, the use of Congo-red injections to induce reticuloendothelial "block" and later by the use of nitrogen mustard and urethane. Most recently, the adrenocorticotrophic hormone (ACTH) was employed, and the results with this material are the subject of the present report.

Nitrogen mustard and urethane were used in the attempt to modify antibody production because of their known effects on reticuloendothelial and lymphocytic tissues. ACTH was tried chiefly because of the investigations of Dougherty and White[9] which showed a reciprocal relation between adrenocortical hormone and lymphoid tissue, and indicated that lymphoid tissue might be an important factor in protein (globulin) metabolism,[10] and in the production of antibodies.[11-13] It is the purpose of this paper to report in a preliminary way our results with ACTH in the treatment of 5 successive cases of acquired hemolytic anemia with abnormal circulating antibodies.

MATERIALS AND METHODS

The 5 cases reported in this study showed the classic features of acquired hemolytic anemia, including the presence of circulating hemagglutinins and a positive Coombs antiglobulin test. In 3 of the patients splenectomy had previously been performed without effect upon the hemolytic process. In 2 cases the hemolytic anemia was "idiopathic," and in the other three, the hemolysis was secondary to generalized lymphosarcoma or chronic lymphocytic leukemia.

Blood counts were performed by the usual methods. Bilirubin determinations were made by the procedure of Malloy and Evelyn.[14] Fecal urobilinogen excretions on pooled, total four-day specimens were measured by the method of Watson,[15] and hemolytic indexes calculated by that of Miller, Singer and Dameshek.[16] Red-cell survival studies on 2 patients were performed by the method of Young, Platzer and Rafferty.[17] Agglutinin titers were established by the method of twofold serial dilutions, using both saline solution and 20 per cent bovine albumin as diluents.[18] Parallel sets of titrations were incubated at 37, 22 and 3°C. Direct Coombs antiglobulin tests were performed in each case, and estimations of adsorbed agglutinin were made by the dilution method of Evans.[19]

Each patient was observed in the hospital for a period varying from twenty-two to forty-two days. In each case base-line studies were made four to eleven days before ACTH therapy was instituted. The ACTH was supplied by the Wilson

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Laboratories and the Armour Company.* The Armour ACTH was administered intramuscularly, usually on a six-hour basis, and the Wilson ACTH subcutaneously on an eight-hour basis. It should be pointed out that weight for weight the Wilson product is stated to be about twice as potent as the Armour preparation.

Case Reports

Case 1. M.G. (N.E.C.H. 49-410), a 40-year-old widow, was admitted to the hospital April 12, 1950. She had undergone splenectomy for massive splenomegaly 1 year prior to admission. The pathological diagnosis was "giant-follicle lymphoma." Two courses of nitrogen mustard therapy and considerable x-ray therapy were then given. Severe anemia developed, for which multiple transfusions were given, averaging 1 per week in the 3 months before admission. About 6 months before entry slight icterus was noted. Two weeks before admission the patient's serum was found to agglutinate all prospective donor erythrocytes. Just prior to admission she was given several transfusions of washed red cells without reaction.

Physical examination revealed a very pale, slightly icteric, poorly nourished woman. There was generalized moderate lymphadenopathy and a well healed splenectomy scar. The liver edge was palpable 3 fingerbreadths below the right costal margin. The remainder of the examination was negative.

Examination of the blood disclosed, in addition to the data presented in Table 1, a white-cell count of 23,150 with 37 per cent neutrophils, 45 to 54 per cent lymphocytes, 16 per cent monocytes, 1 per cent eosinophils and 1 per cent metamyelocytes. The platelets numbered 180,000. The blood smear showed marked spherocytosis and many polychromatophilic macrocytes. Eleven nucleated red cells were noted in a count of 100 leukocytes. Many of the lymphocytes were unusually large and demonstrated bizarre nuclei. Sternal marrow aspiration revealed a normocellular marrow. Megakaryocytes were markedly decreased. There was a diffuse infiltration by lymphocytes and lymphoblasts, which often appeared to be present in nests and sheets of cells. In addition, however, there was a normoblastic hyperplasia, with a "shift to the left" in the erythropoietic series. The fecal urobilinogen excretion average for 4 days was 138 mg. per day, giving a hemolytic index of 76 (normal up to 21) indicating hemolysis approximately 4 times normal. The total protein was 6.5 gm. per 100 cc., with an albumin of 4.7 and a globulin of 1.8 gm. per 100 cc. The serum showed a high concentration of abnormal antibody, and the Coombs antiglobulin test was positive (Table 1). X-ray examination and fluoroscopy of the chest revealed enlarged paratracheal lymph nodes bilaterally, with evidence of enlargement of the hilar nodes.

The patient, whose blood was Group A and Rh positive, received 2000 cc. of washed Group A red cells during the 1st hospital week, and 500 cc of washed Group O cells for erythrocyte

Table 1. *Laboratory Data in Case 1.*

Date	Red-Cell Count	Hemoglobin	Reticulocytes	Serum Bilirubin		Agglutinin Titer at 37°C.	
				Total	Indirect	Autoagglutinin	Isoagglutinin
	×10⁶	gm./100 cc.	%	mg./100 cc.	mg./100 cc.		
4/12/50 (on admission)	0.95	4.2	31.0	2.7	2.2	1:128	1:16
5/13/50 (on discharge)	2.64	9.8	4.8	0.8	—	0	0

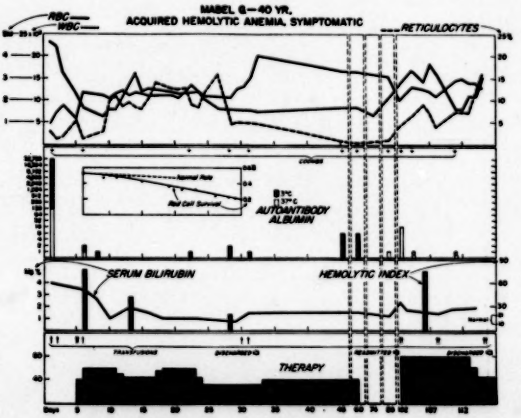

Figure 1. *Effect of ACTH in Case 1.*

*We are indebted to Dr. David Klein of the Wilson Laboratories and to Dr. John R. Mote, of the Armour Company, for their co-operation. Dr. E. B. Astwood supplied ACTH in the early phase of this work.

survival studies, which she tolerated without reaction. Over a 2-day interval, without further transfusions, the red-cell count dropped over 500,000, giving further evidence of rapid hemolysis. ACTH therapy was begun on the 5th hospital day in a dosage of 60 mg. per day* until the 11th day, then 45 mg. per day until the 17th day, 60 mg. per day through the 22nd day and thereafter in a dosage of 30 mg. per day. Agglutinin titers fell during the first 2 days of therapy, with virtual disappearance of agglutinins at 37 and 22° C. and a drop to very low levels at 3°C. Concomitantly, the serum bilirubin fell to normal levels, and the hemolytic index decreased, indicating a marked diminution of hemolysis. The hemoglobin and red-cell count were maintained without transfusion although two transfusions were given just before discharge to achieve higher levels. Red-cell survival studies before discharge showed a rate of destruction only slightly above normal. Reticulocytes did not decrease at first but The serum bilirubin was 2.4 mg. per 100 cc. (2.2 mg. indirect). Serologic examination revealed recurrence of warm agglutinin to a titer of 1:16, although at that time no cold hemagglutinin could be demonstrated.

She was again hospitalized on July 22, and ACTH therapy was reinstituted in a dosage of 60 mg. per day. Within 48 hours, there were no demonstrable agglutinins. Washed red-cell transfusions were given. There was a slow clinical and hematologic improvement, much slower than at the 1st hospital admission, but the patient was discharged on August 4, 1950. Because local reactions to ACTH had developed, she was discharged on Cortisone in a dosage of 50 mg. per day.

The effect of ACTH is shown in Figure 1.

This patient with generalized lymphosarcomatosis and a leukemic blood picture and bone marrow

TABLE 1 (*Concluded*).

DATE	AGGLUTININ TITER AT 3°C.		COOMBS TEST	HEMOLYTIC INDEX	FECAL UROBILINOGEN	SEDIMENTATION RATE
	AUTOAGGLUTININ	ISOAGGLUTININ				
					mg./ day	*mm./ hr.*
4/12/50 (on admission)	1:32,000	1:16,000	Positive	76	138.0	158
5/13/50 (on discharge)	1:1	1:2	Positive	25	78.3	60

instead sought higher levels, later declining to normal. The leukocytosis disappeared, and an actual lymphopenia replaced the original lymphocytosis. The platelets rose to above normal levels. Three repeat bone-marrow examinations showed similar pictures — namely, a normally cellular marrow and a marked diminution in lymphocytes, which now numbered only 13 to 15 per cent of the total number of cells; no nests or sheets were seen. Granulocytopoiesis was now present as well as normoblastic hyperplasia, and the megakaryocytes were increased, with active platelet production. The patient felt greatly improved, looked much better and had no fever. Icterus cleared, and the lymphadenopathy became greatly diminished. A repeat x-ray examination of the chest with fluoroscopy and spot films no longer revealed the previously noted bilateral paratracheal masses.

developed hemolytic anemia with abnormal autoagglutinins. On ACTH therapy there was an almost complete disappearance of abnormal hemagglutinin, together with marked diminution of the signs of hemolysis. Simultaneously, the lymphocytic proliferation was greatly reduced as evidenced by the striking changes occurring clinically and in the blood, bone marrow and chest x-ray film. Cessation of therapy resulted in a complete relapse after a five-week interval. On reinstitution of therapy, a second remission was obtained.

TABLE 2. *Laboratory Data in Case 2.*

DATE	RED-CELL COUNT	HEMOGLOBIN	RETICULOCYTES	SERUM BILIRUBIN		AGGLUTININ TITER AT 37°C.		AGGLUTININ TITER AT 3°C.		COOMBS TEST	SEDIMENTATION RATE
				TOTAL	INDIRECT	AUTO-AGGLUTININ	ISO-AGGLUTININ	AUTO-AGGLUTININ	ISO-AGGLUTININ		
	x10⁶	*gm./100 cc.*	*%*	*mg./100 cc.*	*mg./100 cc.*						*mm./hr.*
4/8/50 (on admission)	1.90	6.1	2.0	2.6	1.6	1:16	1:8	1:256	1:4	Positive	150
5/18/50 (on discharge)	3.62	11.0	0.2	0.4	—	0	0	1:32	1:8	Positive	77

She was discharged on the 33rd hospital day (28th day of therapy), with directions for continued use of ACTH (Armour) in a dosage of 40 mg. per day. The laboratory data on discharge may be noted in Table 1.

On continued therapy at home, the patient showed a sustained clinical and hematologic remission. There was no recurrence of icterus, pallor or lymphadenopathy. Subjectively, she felt very well. The hemoglobin ranged between 10 and 11 gm. per 100 cc., and the red-cell count between 3,100,000 and 3,300,000. A low, variable titer of cold agglutinins remained, but warm agglutinins were not found. The Coombs test remained positive.

On the 72nd day of observation ACTH treatment was terminated because the patient had developed a firm obsession that she was pregnant: she became self-accusatory and somewhat paranoid. Five weeks after discontinuance of therapy, a relapse occurred characterized by recurrence of pallor, icterus and anemia. The hemoglobin value dropped to 6.7 gm. per 100 cc., and the red-cell count to 2,070,000.

*Kindly supplied by Dr. E. B. Astwood and his collaborators.

CASE 2. M. C. (N.E.C.H. 49-196), a 58-year-old man, was admitted to the hospital on April 8, 1950, with complaints of jaundice, weakness and anemia of several weeks' duration. He had previously been known to suffer from a congenital abnormality of the kidneys, secondary pyelonephritis with mild azotemia and moderately severe hypertension. Two months prior to admission, while he was in Florida, fever, malaise, diffuse arthralgia and myalgia developed, and he was found to have generalized lymphadenopathy. The diagnosis of infectious mononucleosis was suspected but not confirmed. Increasingly severe anemia then developed, for which several transfusions were given. Severe transfusion reactions occurred, and, since the course was becoming progressively worse, he was transferred to Boston.

Physical examination showed a semimoribund, disoriented, pale and slightly icteric man. There was a uremic odor to the breath. Funduscopic examination revealed hemorrhages and cotton-wool exudates typical of albuminuric retinitis. There was a generalized lymphadenopathy of moderate

degree. The liver edge was felt 1 fingerbreadth and the spleen 4 fingerbreadths beneath their respective costal margins.

The results of various laboratory examinations are presented in Table 2. The urine showed a +++ test for albumin and a specific gravity of 1.011; numerous leukocytes were present in the sediment. The urinary urobilinogen was normal (but the patient had been on aureomycin prior to entry[20]). The blood nonprotein nitrogen was 68 mg., and the total protein 6.8 gm. per 100 cc., with 3 gm. of albumin and 3.8 gm. of globulin. The serum cholesterol was 87 mg. per 100 cc., with 65 per cent esters, and the alkaline phosphatase was 1 Bodansky unit. The chloride was 99 milliequiv., and the sodium 129 milliequiv. per liter. The cephalin flocculation was ++++, and the thymol turbidity was 1.1. The stools were negative for occult blood. The blood heterophil-antibody reaction was negative. The hematocrit was 20 per cent and the platelets numbered 501,000, the white-cell count was 9900, with 76 per cent neutrophils, 16 per cent lymphocytes, 8 per cent monocytes and 1 nucleated red blood cell per 100 white cells. Examination of the stained smear showed moderate anisocytosis, occasional polychromatophilic macrocytes and occasional spherocytes. Some of the lymphocytes were atypical, but no definitely primitive cells were seen.

Fecal urobilinogen determination on one occasion measured 500 mg. per day. A partial red-cell survival time showed a rapid loss of transfused cells, approximately 66 per cent of the red cells disappearing in 4 days. Frequent transfusions were necessary. Autoagglutinins and isoagglutinins were active at body and room temperatures in albumin mediums only and in saline solution and albumin at ice-box temperatures (Table 2). The direct Coombs antiglobulin test was positive. Bone-marrow aspiration showed slight granulocytic hyperplasia, a slight erythroblastic hyperplasia and rare nests of reticulum cells. Failure to find marked normoblastic hyperplasia and reticulocytosis was attributed to the hemodepressant effects of azotemia.

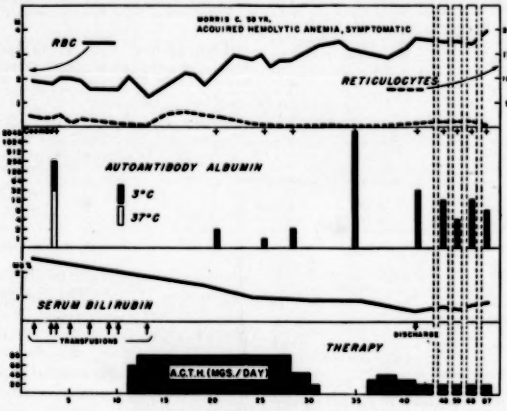

FIGURE 2. *Effect of ACTH in Case 2.*

Biopsy of one of the cervical lymph nodes revealed a malignant proliferation of the lymphoblasts, with disruption of the architecture of the node, diagnosed as a form of lymphosarcoma.

After correction of electrolyte and nutritional imbalance, ACTH (Armour) therapy was given in a dosage of 20 mg. at 6-hour intervals. Almost at once, a dramatic change occurred. The patient suddenly began to feel well and became lucid. The need for transfusions stopped, the icterus diminished, and the red-cell count and hemoglobin began to rise. Recession of lymph nodes and hepatosplenomegaly occurred,

TABLE 3. *Laboratory Data in Case 3.*

DATE	RED-CELL COUNT	HEMOGLOBIN	RETICULOCYTES	SERUM BILIRUBIN	AGGLUTININ TITER AT 37°C.		AGGLUTININ TITER AT 3°C.		COOMBS TEST	SEDIMENTATION RATE
					AUTO-AGGLUTININ	ISO-AGGLUTININ	AUTO-AGGLUTININ	ISO-AGGLUTININ		
	$\times 10^6$	gm./100 cc.	%	mg./100 cc.						mm./hr.
4/11/50 (soon after admission)	2.79	9.5	1.5	0.8	1:4	0	1:8192	1:8192	Positive	10
5/2/50 (on discharge)	3.79	11.7	0.6	0.6	0	0	1:4096	1:512	Positive	3

followed by a sustained rise in red-cell and hemoglobin values and an almost complete disappearance of the hemagglutinin, although the Coombs test remained positive. The sedimentation rate became considerably reduced. Occasional spherocytes persisted. Cessation of therapy for 5 days resulted in a prompt relapse with loss of well-being, tachypnea, reappearance of adenopathy and splenomegaly, rise in sedimentation rate, increase in agglutinin activity and a beginning

drop in red-cell counts and hemoglobin values. Reinstitution of therapy, even at a lowered dosage schedule, again resulted in amelioration of all evidences of relapse. The patient at no time showed any untoward effects from therapy. He was discharged on a maintenance dose of 20 mg. of ACTH daily in two divided doses.

On continued therapy at home, the remission was well sustained both clinically and hematologically. He was ambulatory, showed good color and had no icterus. Lymphadenopathy was minimally present in the axillas, and only the tip of the spleen was palpable. Hemoglobin values ranged about 11.3 gm. per 100 cc., with a red-cell count of 3,500,000.

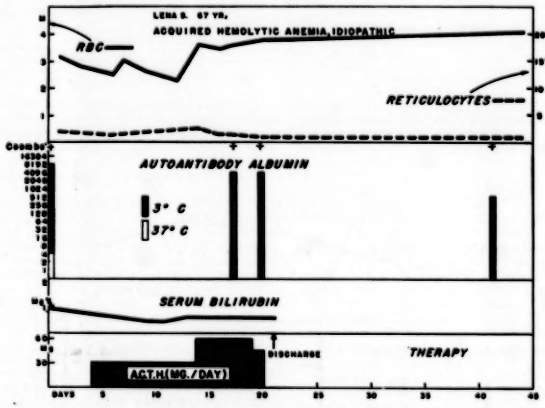

FIGURE 3. *Effect of ACTH in Case 3.*

No recurrence of the warm autoagglutinin had occurred, and the cold agglutinin titer was stable at low levels.

The effect of ACTH is show in Figure 2.

This patient displayed a severe hemolytic anemia in association with a malignant lymphocytic process. Under the influence of ACTH and without splenectomy there was regression of lymphadenopathy and splenomegaly, a progressive rise in the hemoglobin and red-cell count and virtual disappearance of the abnormal hemagglutinin. Temporary cessation of therapy resulted in prompt relapse. On a small maintenance dosage of ACTH this patient maintained an excellent remission and was able to lead a semiactive life. With the exception of a five-day period, he received ACTH for one hundred and five days with no untoward effects.

CASE 3. L. S. (N.E.C.H. 49-38), a 67-year-old woman with a 4-year history of acquired hemolytic anemia of unknown origin and associated with an extremely high concentration of cold hemagglutinin, was admitted to the hospital on April 11, 1950. Splenectomy had been performed 3 years previously, with little or no effect. Therapy in the 2 years prior to admission had consisted of occasional blood transfusions as required.

Physical examination revealed an obese, well developed woman with moderate pallor of the skin and mucous membranes. There was no icterus, hepatomegaly or lymphadenopathy. A well healed splenectomy scar was present. The remainder of the physical examination was negative.

Examination of the blood disclosed, in addition to the data presented in Table 3, 1,700,000 platelets and a white-cell count of 4100. The blood smear demonstrated many spherocytes. The serum showed an extremely high concentration of cold hemagglutinin, with only a slight concentration of warm antibody. The Coombs antiglobulin test was positive (Table 3).

ACTH (Wilson) therapy was begun on the 4th hospital day and was maintained at 30 mg. per day until the 14th day and at 60 mg. per day from the 14th through the 19th day, when the dosage was decreased pending discharge. Demonstrable agglutinins disappeared at 37°C., almost completely disappeared at 22°C. and diminished slightly to moderately at 3°C., with decreases of from 1-tube to 4-tube dilutions. There was a moderate rise in red-cell count and in hemoglobin (1,000,000 and 2.2 gm. per 100 cc. respectively) and the reticulocytes fell to normal levels. Subjectively, the patient noted a greatly increased sense of vigor and well being.

Table 3 lists laboratory data at discharge, and Figure 3 shows the effect of ACTH.

Three weeks after cessation of therapy, the patient had maintained both clinical and hematologic improvement. Subjectively, she continued to feel well. There was no pallor or icterus. The hemoglobin had risen still further to 12 gm. per 100 cc., and the red-cell count to 4,100,000. Serologically, the cold agglutinin titer had further decreased, and no agglutinin was demonstrable at 37°C.

This patient with idiopathic acquired hemolytic anemia showing a high titer of cold hemagglutinin was on ACTH therapy for fifteen days. It is probable that the ACTH dosage (30 mg. per day during most of the course) was too low and the duration of therapy too brief for a completely adequate trial. However, even with this amount of therapy, there was a complete disappearance of agglutinin at 37°C., and a slight though definite decrease of cold hemagglutinin together with a rise in red-cell count and hemoglobin. Subjectively, there was

definite improvement. Improvement was maintained for three weeks after discontinuance of therapy. At this point, the patient left the State and could no longer be observed.

CASE 4. R. W. (N.E.C.H. 43-333), a 43-year-old farmer, was first seen in August, 1949, with complaints of icterus, pallor and weakness of 2 months' duration. Three months previously a severe upper respiratory infection had developed, lasting for about 1 week. Examination revealed pallor, icterus and splenomegaly, and the blood showed marked anemia with spherocytosis, polychromatophilic macrocytosis and intense reticulocytosis. There was bilirubinemia at a level of 3.4 mg. per 100 cc. and a high fecal urobilinogen output. A strongly positive direct Coombs test was present, together with a serum autoagglutinin that was most active in bovine albumin and at 37°C. (1:256). No fundamental or associated disorder was demonstrated, and the diagnosis of acquired hemolytic anemia, idiopathic type, was made.

TABLE 4. *Laboratory Data in Case 4.*

DATE	RED-CELL COUNT	HEMOGLOBIN	RETICULOCYTES	SERUM BILIRUBIN		AGGLUTININ TITER AT 37°C.	
				TOTAL	INDIRECT	AUTOAGGLUTININ	ISOAGGLUTININ
	$\times 10^6$	gm./100 cc.	%	mg./100 cc.	mg./100 cc.		
4/20/50 (on admission)	1.91	7.4	3.9	2.9	2.3	1:1	0
5/18/50 (on discharge)	3.81	12.1	9.8	1.0	—	0	0

A course of nitrogen mustard therapy failed to influence agglutinin production. Splenectomy was performed on August 30, with only a transitory effect on the hemolytic process. A severe upper respiratory infection necessitated readmission in October, when hemolysis was found to be greatly intensified. A series of intravenous injections of urethane failed to influence agglutinin production. After a stormy course, the patient recovered sufficiently to permit resumption of limited physical activity. Red-cell counts hovered at about 2,000,000, with hemoglobin determinations in the vicinity of 8 gm. Continued hemolysis was evidenced by pallor, icterus, reticulocytosis, normoblastosis and a high fecal urobilinogen excretion. Early in February, 1950, the rate of hemolysis decreased simultaneously with a diminished titer of serum agglutinin. Although further transfusions were no longer necessary the patient continued to have marked anemia, to which he seemed well adjusted. He was rehospitalized on April 20 for a trial of ACTH therapy.

Physical examination revealed only pallor and slight icterus.

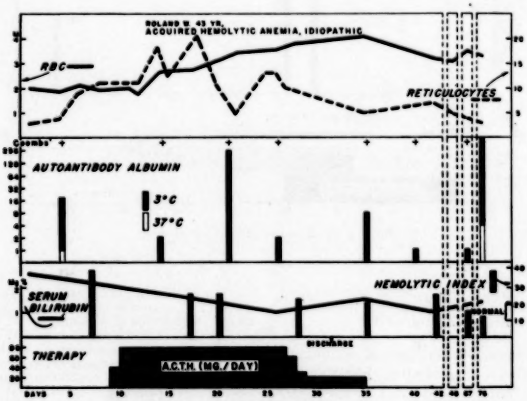

FIGURE 4. *Effect of ACTH in Case 4.*

TABLE 5. *Laboratory Data in Case 5.*

DATE	RED-CELL COUNT	HEMOGLOBIN	RETICULOCYTES	SERUM BILIRUBIN		AGGLUTININ TITER AT 37°C.	
				TOTAL	INDIRECT	AUTOAGGLUTININ	ISOAGGLUTININ
	$\times 10^6$	gm./100 cc.	%	mg./100 cc.	mg./100 cc.		
On admission	1.25	3.5	0.8	2.3	1.5	0	0
On discharge	2.90	8.0	3.2	1.2	—	0	0

Laboratory data are presented in Table 4. The urine showed hemosiderin granules in the sediment. The total protein was 7.3 gm. per 100 cc. (albumin of 3.6 gm. and globulin of 3.7 gm). The cephalin flocculation was +++. The platelets numbered 891,000, and the white-cell count was 29,000, with 63 per cent neutrophils, 30 per cent lymphocytes, 5 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils.

TABLE 4 (*Concluded*).

DATE	AGGLUTININ TITER AT 3°C.		COOMBS TEST	HEMOLYTIC INDEX	FECAL UROBILINOGEN	SEDIMENTATION RATE
	AUTOAGGLUTININ	ISOAGGLUTININ				
					mg./day	*mm./hr.*
4/20/50 (on admission)	1:16	1:8	Positive	38	170	135
5/18/50 (on discharge)	1:2	1:1	Positive	25	156	90

Examination of the blood smear demonstrated marked spherocytosis and polychromatophilic macrocytosis; 38 nucleated red cells per 100 white cells were noted. The autohemagglutinin was weakly active in albumin at 37°C. Autoagglutinins and isoagglutinins were more active at 3°C. in both saline solution and albumin.

After a period of observation the patient was given ACTH (Armour), receiving 20 mg. every 6 hours. For the last 48 hours of his hospital stay he received ACTH (Wilson), 20 mg. every 8 hours. He tolerated the therapy well, showing no fluid retention, excessive weight gain or hypertension. He was subjectively much improved. A definite hematologic remission occurred, as indicated by a drop in serum bilirubin to normal, a marked decrease in fecal urobilinogen output and an increase in red-cell count and hemoglobin (Table 4). A striking feature was a brisk reticulocytosis beginning on the 3rd day of therapy.

The patient was discharged on maintenance ACTH (Wilson) therapy in a dosage of 20 mg. per day. This was discontinued after 1 week. During the next 6 weeks he continued to show an excellent clinical and hematologic remission, but a slight though definite rise in warm autoagglutinin of the serum suggested beginning relapse. However, these agglutinins disappeared spontaneously, and he remained well 11 weeks after cessation of therapy (Fig. 4).

This patient with idiopathic acquired hemolytic anemia had failed to respond to either splenectomy or nitrogen mustard therapy. After ACTH therapy the icterus disappeared, and the red-cell count and hemoglobin rose steadily. An unusual feature was an intense normoblastosis and reticulocytosis of the peripheral blood after which the red-cell count rapidly reached virtually normal levels. The return of the warm hemagglutinin suggested impending relapse, but this disappeared spontaneously.

CASE 5. A. M. (N.E.C.H. 60-015), a 67-year-old farmer, was admitted to the hospital on June 14, 1950, with the splenomegaly and an elevated white-cell count (27,050), the differential count showing 87 per cent lymphocytes, some of which were immature. Four transfusions of whole blood were given, with only a slight rise in the red-cell count, after which he was transferred to this hospital.

Physical examination disclosed an obese man with marked pallor and slight icterus of the scleras. There was moderate enlargement of the axillary and cervical lymph nodes. A harsh systolic murmur was heard over the precordium. The blood pressure was 150/65. The liver edge was felt 3 finger-breadths below the right costal margin, and the spleen extended to the umbilicus. There was slight pitting edema of the ankles.

Examination of the blood showed, in addition to the data presented in Table 5, a platelet count of 233,750 and a white-cell count of 21,300, with 12 per cent neutrophils, 9 per cent monocytes and 79 per cent adult lymphocytes. Occasional spherocytes and macrocytes were seen. The blood nonprotein nitrogen was 51 mg. the total protein 6.1 gm. (with an albumin of 4.1 and a globulin of 2 gm.), the cholesterol 98 mg., with 62 per cent esters, and the uric acid, 6 mg. per 100 cc. The cephalin flocculation was ++++, and the thymol turbidity was 2.1 units. Sternal-marrow aspiration showed marked infiltration of the marrow with mature lymphocytes.

The diagnosis of chronic lymphocytic leukemia with a superimposed hemolytic process was made. The hemolytic component was confirmed by the demonstration of a high fecal urobilinogen output, a positive Coombs test and the detection of an autohemagglutinin in the patient's serum strongly active at ice-box temperature in both saline solution and albumin. Studies of the red-cell survival time begun on June 17 showed a disappearance of 50 per cent of the transfused cells in 5 days.

After 5 days of observation, ACTH (Wilson) therapy was begun in a dosage of 20 mg. every 8 hours. This dosage was continued for a period of only 8 days since it soon became apparent that a high or fixed schedule for ACTH was impossible to maintain because the patient showed excessive fluid retention, with incipient pulmonary edema. Despite salt restriction, digitalization and the use of mercurial diuretics, this remained a troublesome problem throughout the hospital stay. A comparison of transfusion requirements on a weekly basis, however, indicated a definite decrease in the need for transfused cells (Table 6).

There was a reduction in the bilirubinemia to near normal levels, diminution in the fecal urobilinogen output and a decrease in abnormal hemagglutinin. Because of the possibility that some of the transfused blood was "sequestered"

TABLE 5 (*Concluded*).

DATE	AGGLUTININ TITER AT 3°C.		COOMBS TEST	HEMOLYTIC INDEX	FECAL UROBILINOGEN	SEDIMENTATION RATE
	AUTOAGGLUTININ	ISOAGGLUTININ				
					mg./day	*mm./hr.*
On admission	1:32	1:8	Positive	57	145	158
On discharge	1:4	1:2	Positive	24	104	27

complaints of weakness and fatigue. Six months previously fatigue, dyspnea, palpitation and weight loss developed. Two weeks prior to admission, pallor and icterus were noted, and the patient was hospitalized. Examination revealed in the enlarged spleen, x-ray therapy over the spleen was also administered during the course of ACTH therapy. There was a prompt reduction in the total leukocyte and lymphocyte counts, but the size of the spleen diminished

only slightly. The patient was discharged on July 19, on a maintenance dosage of 10 mg. of ACTH twice daily.

Laboratory data on discharge are recorded in Table 5, and Figure 5 shows the effect of ACTH.

This man with chronic lymphocytic leukemia developed severe hemolytic anemia necessitating almost daily transfusions. There was evidence of an autohemolytic mechanism. ACTH therapy was hampered by a tendency to excessive fluid retention. The rapid disappearance of transfused cells, together with the presence of marked splenomegaly, suggested an additional factor of splenic sequestration of red cells, and x-ray therapy to the spleen was accordingly administered. The need for transfusions gradually lessened. At the time of the patient's discharge from the hospital the various indications of increased hemolysis had diminished greatly. Three weeks later the patient maintained his blood counts although no transfusions had been given.

TABLE 6. *Effect of ACTH on Tranfusion Requirements.*

PERIOD	ACTH DOSAGE	NO. OF TRANSFUSIONS	AVERAGE RED-CELL COUNT
	mg.		x10⁶
6/14–6/18	0	4	1.2
6/19–6/25	400	5	1.9
6/26–7/2	250	6	1.7
7/3–7/9	270	3	2.0
7/10–7/16	250	0	2.4

DISCUSSION

Acquired Hemolytic Anemia and Autoimmunization

As the result of many observations during the past dozen years, it has become clear that most cases of hemolytic anemia of the "acquired variety" are due to the development of autoantibodies, which result in the injury and subsequent hemolysis of mature red blood cells.[21] The life span of the average red cell within the patient's circulation becomes considerably shortened. This holds true not only for the patient's own red cells but also for normal red cells, which are introduced by transfusion.[22] The means by which autosensitization is induced is obscure, although it is clear that certain virus infections and certain proliferative disorders of the white cells, notably of the lymphocytic variety, result not infrequently in the appearance of autoantibodies, and in hemolytic anemia. Do these diseases stimulate a mechanism by which some of the patient's own red blood cells become antigenic and produce autoantibodies? This is quite unknown. The actual site of antibody formation is also obscure although one may speculate with some reason that it is the reticuloendothelial system,[5] the lymphoid system[6] or the system of plasma cells.[23, 24] The occurrence of hemolytic anemia in association with chronic lymphocytic leukemia, lymphosarcoma and reticulum-cell sarcoma may indicate that the proliferating abnormal tissue itself produces an abnormal globulin (antibody), which has the capacity to affix itself to the red blood cell and thus to cause its early destruction. This

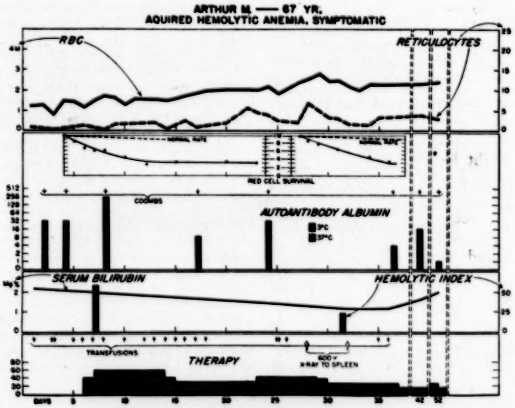

FIGURE 5. *Effect of ACTH in Case 5.*

also suggests that careful search for a fundamental disease should always be made in every case of acquired hemolytic anemia, even when the process appears to be wholly "idiopathic." The apparent differences between "idiopathic" and "symptomatic" forms of acquired hemolytic anemia appear to be losing their former rigidity, for present indications show that they are both based on autoimmunization.

Previous Attempts to Influence Autoimmunization

Most of the earlier therapeutic methods centered on splenectomy as the chief means for reducing or even removing antibody activity. The spleen is not only the largest single compact unit of reticuloendothelial cells but the largest lymphoid organ of the body. Many cases of acquired hemolytic anemia have been dramatically cured by splenectomy, and indeed some of our early cases showed a complete cessation in antibody activity after this operation. As our experience has accumulated, however, we have noted that splenectomy may or may not be wholly beneficial; in fact, most of our cases in the past five years have shown a persistence of autoantibody after splenectomy even though the patient might be in a state of partial or even complete remission. Many cases have shown little or no effect with splenectomy, thus bringing up the necessity of exploring other therapeutic methods. Gradually, this has centered about the possibility of causing either the elimination of abnormal antibody or the inhibition of antibody. Attempts to inhibit antibody by the use of plasma or whole-blood transfusions or by other means have proved unsuccessful.

Acting upon the assumption that the reticuloendothelial system might be the site of antibody formation, we have used in previous cases repeated injections of large amounts of Congo red in the attempt to "block" the reticuloendothelial system, spray x-ray therapy in the attempt to reduce activity of this system and, more recently, nitrogen mustard. The first two methods were completely without effect in patients in whom splenectomy had first proved unsuccessful, but the use of nitrogen mustard intravenously was followed in 1 case by a striking response. Four cases of acquired hemolytic anemia with autoantibody were treated with a regular course of nitrogen mustard intravenously. In the only 1 showing a beneficial effect (N.E.C.H. 40-272) there was a striking reduction and then a complete disappearance in antibody simultaneously with a complete remission in the blood picture. The patient has remained completely well for over a year. The negative results in the other 3 cases led us to suspect that the reticuloendothelial system, the tissue most affected by nitrogen mustard, might not be at fault in the hemolytic process, and that it was perhaps the lymphoid apparatus that should be attacked.

Urethane was used in 1 of our cases because of the possibility that it might reduce lymphoid tissue activity, but there was no effect. With the advent of a supply of ACTH, a trial of this material seemed highly desirable, particularly in view of its known effects on lymphoid tissue and on antibody formation. This seemed particularly advisable in the cases of acquired hemolytic anemia that had a neoplastic type of lymphocytic proliferation as the fundamental background especially since we had previously demonstrated a beneficial effect in certain cases of lymphocytic leukemia treated with ACTH.[25]

ACTH and Antibody Formation

In 1944 Dougherty, White and Chase[11] reported that under conditions of increased pituitary-adrenocortical activity, antibodies became increased in the circulation and that these were presumably produced as a result of lymphocytic dissolution. Subsequently, conflicting reports on this point have appeared. Eisen et al.[26] and Fischel, LeMay and Kabat,[27] using more rigorous immunochemical technics and single purified antigens, reported the failure of adrenocortical extract and ACTH to enhance antibody titers. Indeed, Fischel and his co-workers noted a slight decrease in antibody although a fall in lymphocytes did occur in his animals. The present investigation with clinical material has considerable bearing in this connection. If the studies of Dougherty, White and Chase were applicable here, the administration of ACTH should lead to at least a transitory increase in the autoagglutinin titer and to an intensification of hemolysis. However, both previous work[28] and that in progress[29] has failed to demonstrate any alteration of the concentration of various naturally occurring and pathologic hemagglutinins upon *short-term* administration of ACTH or Cortisone. Thus, the results of these acute experiments seem to conform more with the observations of Eisen and his associates than with those of Dougherty and others.

Since the *long-term* administration of ACTH resulted in unquestionable diminution in the agglutinin activity, as well as in clinical improvement, it is certain that some profound alteration in the abnormal antigen-antibody system must have occurred. Two possibilities suggest themselves: ACTH might affect antigen antibody reactions, by inhibiting their union, or it might interfere with the production of the antibody. The type of agglutinating system used in serum titrations, unfortunately, permits no answer to these fundamental questions, for effective antibody *activity* rather than actual antibody *concentration* is measured. Thus, a significant fall in agglutinating titer could be attributed to inhibition of antigen-antibody union as readily as it could to diminution in antibody concentration.

Nevertheless, the clinical observation of marked lymphoid regression, together with falling agglu-

tinin titers, suggests a gradual depletion of the tissue site for antibody production with the resultant diminution in serum antibody. This seems to be in agreement with the deficiency in antibody production observed in animals depleted of lymphoid tissue by means of x-rays.[20, 21]

Thus, our observations to date indicate that the continued administration of ACTH in cases of hemolytic anemia with autoimmunization results in a marked reduction in antibody activity, possibly owing to diminished antibody production as a result of lymphoid regression.

Practical Considerations

Perhaps of most immediate significance is the ability of ACTH to inhibit in varying degree the hemolytic process, whether idiopathic or secondary to lymphocytic proliferation. This was observed in 5 consecutive cases of acquired hemolytic anemia with agglutinins. Within a few days of the institution of therapy in the first 4 cases, there was a definite reduction in demonstrable agglutinin activity. Concomitantly, there was a progressive clinical and hematologic improvement, as manifested by rises in red-cell count and hemoglobin and a decreased necessity for blood transfusions. More direct evidence for the control of the hemolytic process included the disappearance of icterus, a fall in serum bilirubin and, in the 1 case measured, the development of an almost normal survival time of transfused erythrocytes. That the relation between ACTH therapy and the decrease in demonstrable agglutinin and, in turn, between agglutinin level and hemolytic activity was not fortuitous is suggested by the fact that in 2 of the patients (Cases 1 and 2) in whom ACTH therapy was discontinued, a rise in agglutinin titer together with reactivation of hemolysis occurred.

It is thus evident that ACTH may be effective in producing a remission in cases of acquired hemolytic anemia, probably by producing a fundamental alteration in the abnormal immunologic mechanisms that are of primary pathogenic significance in this disease.

In addition to the suppression of hemolysis, it is probable that ACTH also affected these cases favorably, by either stimulating regeneration of red cells or hastening their release into the peripheral circulation. This is in line with our previous observations in leukemia, which suggested a direct stimulatory effect upon bone-marrow megakaryocytes and nucleated red blood cells by ACTH. Cases 3 and 4 showed marked increase in red-cell count with only slight reduction in the degree of hemolysis.

The findings recorded here suggest that ACTH offers a method — albeit a temporary one — for attacking antibody formation and thus for controlling the fundamental abnormal process in acquired hemolytic anemia. It is within the realms of possibility that the continued and judicious administration of these hormones will lead finally to an exhaustion of the mechanism that produces abnormal agglutinin and thus to control of the disease. In chronic lymphocytic leukemia and lymphosarcoma with hemolytic anemia, it appears from our findings that at least temporary control of the hemolytic process has been rendered much more effectual than was previously possible. This is particularly gratifying since there may be a simultaneous regression of lymphocytic proliferation. In the idiopathic cases, it is possible that the use of ACTH as a preliminary measure, and as a means of reducing abnormal antibody, possibly to be followed later by splenectomy or with some other measure such as the use of nitrogen mustard, will lead to a better control of this serious disease than has hitherto been possible.

Summary and Conclusions

Five cases of acquired hemolytic anemia treated with adrenocorticotrophic hormone (ACTH) are presented. Three cases were of the "symptomatic" variety, being associated with lymphosarcoma or lymphocytic leukemia, and the other 2 were "idiopathic." All cases had circulating hemagglutinins and a positive Coombs test. Each patient received intensive ACTH therapy followed by maintenance therapy in all cases but 1.

Four of the 5 patients showed almost complete remissions of the hemolytic process. Simultaneously, there was disappearance of "warm" hemagglutinin and marked diminution of cold hemagglutinin. The Coombs test remained positive in all cases.

One case was complicated by excessive fluid retention, which necessitated a lower daily ACTH administration than that used in the other cases; this patient's response was slower. The only other complication that could be attributed to ACTH administration was the development of a mild psychosis in Case 1.

Relapses in the hemolytic process occurred shortly after cessation of therapy in 2 cases (Cases 1 and 2), and resumption of therapy resulted in a second remission.

The role of abnormal agglutinins in the pathogenesis of acquired hemolytic anemia is discussed. It is suggested that the favorable effect exhibited by ACTH on this type of hemolysis is dependent upon a disruption of agglutinin production presumably by regression of lymphoid tissue, in which agglutinin may be produced. The stimulatory effect of ACTH upon bone-marrow activity may result in a further beneficial effect.

The administration of ACTH in acquired hemolytic anemia associated with circulating hemagglutinins results in the development of well defined remissions.

Remissions may be induced in both "symptomatic" and "idiopathic" cases. Remissions may be continued by the use of maintenance therapy.

The disappearance or diminution of hemagglutinin activity suggests that ACTH exerts its favorable influence by altering the pathologic antigen-antibody system. Existing evidence indicates that this is probably due to decreased antibody production by lymphoid tissue.

Since writing the above, patients M. G. and M. C. (Cases 1 and 2) have died of their fundamental disease. Three other cases of acquired hemolytic anemia, idiopathic type, have been treated, and all have shown dramatic responses. In 3 cases (Cases 2, 4 and 5) the Coombs antiglobulin test became negative. Thus, in 8 consecutive cases, mild or extremely severe idiopathic or symptomatic, a marked beneficial effect on the hemolytic process took place. In recent cases, Cortisone (Merck) has been found useful in tablet form for continued maintenance therapy.

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ACUTE SURGICAL EMERGENCIES OF THE ABDOMEN IN PREGNANCY

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THE experiences of the Boston Lying-in Hospital with acute surgical emergencies from 1916 to 1939 have been reported.§ Because of the subsequent introduction of newer methods of therapy and in order to answer questions concerning the effect of pregnancy on acute abdominal conditions and the effect of acute abdominal conditions on pregnancy, it has been thought advisable to add the experiences of the Boston Lying-in Hospital with acute surgical emergencies for the years 1939–1948 to those already published.

As in the previous report, ectopic pregnancies and traumatic ruptures of the uterus during delivery have been excluded.

Table 1 lists the various acute abdominal conditions in pregnant patients encountered at the Boston Lying-in Hospital from 1939 to 1948. During the same period there were 26,341 deliveries. These figures do not pretend to represent the total incidence of abdominal emergencies during those years, since some patients were doubtless treated at other hospitals. The incidence of acute abdominal conditions for the years 1916–1948, during which there were 92,772 deliveries, is shown in Table 2, which has been derived by the addition of the present series to that previously reported.

TABLE 1. *Acute Abdominal Conditions in 26,341 Deliveries, 1939–1948.*

CONDITION	NO. OF CASES
Acute pancreatitis	0
Perforated ulcer	0
Acute gall-bladder disease	4
Intestinal obstruction	3
Incarcerated hernia	0
Acute appendicitis	16
Ovarian cyst	11
Spontaneous rupture of uterus	9
Fibroid, with acute degeneration or twisted pedicle	6
Total	49

ACUTE PANCREATITIS

As noted in the previous report, cases of acute pancreatitis complicating pregnancy have been reported in the literature, but no patient with this condition appears in the records of the Boston Lying-in Hospital from 1916-1948.

PERFORATED ULCER

Gastric and duodenal ulcers are, of course, far less common in the female than in the male, and the tendency of these lesions to become asymptomatic during pregnancy is now well recognized. It is therefore not surprising that this additional ten-year period still fails to disclose any patient with a perforated gastric or duodenal ulcer admitted to this hospital.

TABLE 2. *Acute Abdominal Conditions in 92,772 Deliveries, 1916–1948.*

CONDITION	NO. OF CASES
Acute pancreatitis	0
Perforated ulcer	0
Acute gall-bladder disease	7
Intestinal obstruction	4
Incarcerated hernia	1
Acute appendicitis	40
Ovarian cyst	21
Spontaneous rupture of uterus	23
Fibroid, with acute degeneration or twisted pedicle	13
Total	109

ACUTE GALL-BLADDER DISEASE

In the period under study 23 patients had symptoms attributable to cholecystitis or cholelithiasis. Four had frank acute cholecystitis, but all cases subsided promptly on conservative treatment and no patient was subjected to operation during pregnancy. All went to term uneventfully.

The management of these 4 cases of acute cholecystitis reflects the fact that our treatment of this condition in pregnancy has tended to be more conservative than it might have been in nonpregnant women. The increased technical difficulties of cholecystectomy in the presence of a large uterus, the possibility of miscarriage or premature labor when surgical trauma is added to the presence of an intra-abdominal inflammatory process and our success in carrying these patients to term, without further trouble once the acute process has subsided, have tended to influence us toward conservative treatment. Obviously, failure of the acute symptoms to subside promptly would be a positive indication for surgery that would outweigh this conservative tendency.

INTESTINAL OBSTRUCTION

This condition remains a rare surgical complication of pregnancy, but there were 3 instances of small-bowel obstruction in this ten-year period, as compared with 1 in the previous report.

The principles of management of obstruction in the small intestine are not altered in the presence

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§Smith, J. A., and Bartlett, M. K. Acute surgical emergencies of abdomen in pregnancy. *New Eng. J. Med.* 223:529-531, 1940.

of pregnancy. However, the frequency of vomiting during pregnancy and the presence of the enlarged uterus may serve to confuse the clinical picture, and the displacement of the intestines by the fundus may make the interpretation of the gas pattern, as visualized on x-ray examination, difficult. The details of these 3 cases are given below.

CASE 1. A 25-year-old para I was admitted to the hospital on September 30, 1940, in the 7th month of pregnancy, with a 4-day history of crampy epigastric pain, nausea, vomiting and obstipation. The abdomen was slightly distended, with active, high-pitched peristaltic sounds. A diagnosis of intestinal obstruction was made. In spite of attempts to decompress the bowel by tube from above, the distention increased, and a laparotomy was performed. At operation a band obstruction of the midportion of the jejunum was found and released. Twelve hours after operation, after a brief, violent labor, a 4-pound infant was delivered. Twelve hours later the patient had a bowel movement and made an uneventful recovery, as did the baby. A 10-year follow-up report on this patient showed no further obstructive symptoms and 3 subsequent uneventful pregnancies.

CASE 2. A 45-year-old para I entered the hospital on August 10, 1946, when she was 5½ months pregnant. She was known to have a large fibroid uterus, and every effort was being made to carry her along as far as possible in the hope of getting a viable baby. In the morning of admission irregular crampy abdominal pain and nausea were noted, and she was sent to the hospital for observation. The large pelvic mass, which previously could be displaced upward, was no longer movable. Abdominal distention developed in the next 48 hours, with obstipation in spite of repeated enemas. The temperature and white-cell count remained normal. On the 3rd day after admission a tender area developed at the top of the fundus. A diagnosis of degenerated fibroid was made, and laparotomy carried out. The obstruction was due to a knuckle of small bowel adherent to a degenerated fibroid. This was freed. A subtotal hysterectomy was done after the delivery of a fetus weighing 1 pound, 6 ounces, by hysterotomy. The infant survived only 2 hours. The mother recovered uneventfully.

CASE 3. A 34-year-old para I was admitted to the hospital on September 10, 1946, in her 4th month of pregnancy for an elective myomectomy because of evidence of degeneration of a fibroid. On the 6th postoperative day, signs of intestinal obstruction developed, and a Miller–Abbott tube was passed. The signs and symptoms of obstruction were relieved but returned each time the tube was taken off suction. On the 16th postoperative day the abdomen was reopened. A loop of small bowel was found adherent to the myomectomy wound, with obstruction at this point. This was released, and the patient made a smooth convalescence from the operation. However, she was readmitted 1 month later and a macerated fetus was delivered.

HERNIA

Hernia continues to be an infrequent abdominal emergency in pregnancy. Two inguinal hernias were successfully repaired because of increasing pain, but no case of incarceration requiring surgical intervention was encountered in this ten-year period.

APPENDICITIS

As might have been expected, appendicitis was the cause of the largest number of acute surgical emergencies as it was in the previous study. Though the results of treatment of appendicitis during pregnancy during the past ten years are good, the condition is still a very important problem. Because many pregnant women complain of minor abdominal pain there is still some tendency to consider the possibility of appendicitis later than in a nonpregnant patient. The signs of appendicitis may also be somewhat altered by pregnancy. In the later stages the cecum and hence the appendix are often forced from their usual position by the enlarging uterus, and local tenderness may be found much higher than McBurney's point. Muscle spasm may be very slight or absent because of the enlarging abdomen. One should also remember the physiologic leukocytosis of pregnancy, which may give a false impression of the presence of an inflammatory reaction.

Because of the high mortality to both fetus and mother associated with rupture of the appendix, extreme care has been exercised to explore the abdomen in all suspicious cases. This has led to a higher incidence of errors in diagnosis than is desirable, but no appendix has been allowed to rupture under observation. Nor have any of these negative explorations led to miscarriage or premature labor.

In all, 22 patients were operated upon with a preoperative diagnosis of acute appendicitis without maternal mortality. In 6 cases the diagnosis proved to be erroneous, 5 patients having no demonstrable lesion and 1 having hemorrhage into an old hydrosalpinx. In the 5 cases the appendix was removed, and in the sixth case the appendix and the tube were removed. All 6 patients went to term and had uneventful deliveries.

Of the 16 cases in which the diagnosis was correct 12 had unruptured appendixes, which were removed without drainage. One patient was at term and went into labor sixty hours after operation. Two patients, who were four weeks and eight weeks from term, respectively, went into labor forty-eight hours after operation. Of the remaining 9 patients 2 were seven months, 3 were six months, 2 were five months, 1 was three months, and 1 was two months pregnant. All 9 went to term. In all 12 cases the babies survived.

It is interesting to compare these figures with our previous report, in which there were also 16 cases of acute appendicitis without rupture. In 11 cases drainage was not performed, and 4 patients miscarried or went into premature labor shortly after operation. In 5 of the 16 cases drainage was done, and 4 of these patients promptly miscarried or went into premature labor.

Four patients had ruptured appendixes at the time of admission to the hospital. Three had generalized peritonitis, and 1 a localized abscess that was mistaken for a twisted ovarian cyst. The duration of symptoms in these patients was four, five, seven and fourteen days. All were operated upon. Drainage of the appendiceal area was done in all, the appendix being removed in only 1. Wound sepsis developed in 2 cases, and pelvic abscesses

on the left side requiring later drainage, in 2. All patients recovered. One of these patients, who was in the seventh month of pregnancy at the time of operation, was delivered a month later. One was admitted in labor at seven months and was delivered promptly. The third, at eight months, went into labor twenty-four hours after operation. All 3 babies survived. The fourth patient, five months pregnant at the time of operation, miscarried ten days later.

Contributing to the survival of these mothers with ruptured appendixes and generalized peritonitis, as contrasted with the high mortality of this condition in our previous report, are a better understanding of electrolyte balance, the use of fluids parenterally, whole-blood transfusion and the antibiotics.

The following case does not fit into the above categories:

A 32-year-old para II was 3 months pregnant when admitted to the hospital because of generalized abdominal pain and tenderness of 3 days' duration. She had a temperature of 101.4°F. and a white-cell count of 14,000. One month previously a laparotomy had been performed at another hospital for abdominal pain. A multiple fibroid uterus was found. Because she was pregnant, nothing but an appendectomy was done.

After the present admission the signs and symptoms persisted and were attributed to degeneration of one or more fibroids, and exploratory laparotomy was done. Peritonitis originating from the appendiceal stump was found, and a drain was placed down in this area. The patient recovered without complication and had a normal delivery at term.

Ovarian Cyst

The general policy toward ovarian cysts discovered during pregnancy is to remove them at once. The impossibility of determining the exact nature of a cyst by any other means and the chance of rupture, torsion or other complications during pregnancy, labor or the puerperium appear to outweigh the hazards of laparotomy and of subsequent miscarriage or premature labor. Some cysts go undetected until acute symptoms of rupture or torsion develop. Such situations, of course, demand prompt intervention.

In the present study 11 patients with ovarian cysts were operated on during pregnancy, with no maternal mortality. Two of these operations were done as emergencies, 1 for a dermoid cyst with twisted pedicle at four months, with subsequent uneventful delivery at term, and 1 at eight months for a fibroma of the ovary with infarction, a viable infant being delivered two days later.

In 2 patients adnexal masses were discovered early in pregnancy; the patients were carried to term and were then delivered by cesarean section because of obstruction of the pelvic outlet by the tumor. A concomitant salpingo-oophorectomy was done in each case. The tumor in 1 was a dermoid cyst, and in the other a fibroma of the ovary.

The remaining 7 patients had elective operations at two, three, three, three and a half, four, four and seven months. In 1 patient a resection of the cyst from the ovary, and in the remaining 6 a salpingo-oophorectomy was performed. Three of the cysts were dermoids, 2 were simple serous cysts, 1 was an endometrial cyst, and 1 was a paraovarian cyst. The patient operated upon at seven months went into premature labor, and the baby did not survive. One patient, operated on at three months, was delivered of a stillborn child at term. Two patients did not return to this hospital for delivery, and the fate of the pregnancy is unknown. The remaining 3 patients were delivered uneventfully at term.

In retrospect, it might have been wiser to operate earlier on the patient who was subjected to surgery at seven months and on the 2 patients who were carried to term. The ovarian tumor was discovered at the first prenatal visit in each of these patients and the operation could have been done at a time of election. This might well have resulted in a viable child in the first case and might have avoided cesarean section in the other 2.

Spontaneous Rupture of the Uterus

Spontaneous rupture continues to be the commonest surgical emergency involving the uterus itself. In the ten-year period under study, 9 cases were encountered, with 1 death.

In 3 cases the rupture was at the site of a previous cesarean section. In 2 of the 3 cases there were no symptoms, and the rupture was discovered when the repeat section was done. In both cases a living child was obtained, the rupture was repaired and the uterus left in, and both mothers survived. The third patient had been delivered of her first child by cesarean section because of a pelvic deformity following a fracture of the pelvis. In her second pregnancy she had a precipitate normal delivery of a 6-pound child twenty-four hours before the planned repeat section. For this reason it was decided in her third pregnancy to allow her to go into labor. After twelve hours of mild labor severe abdominal pain and shock developed. At laparotomy a rupture of the scar was found, a stillborn infant removed, from the abdominal cavity, and a hysterectomy done. This patient also survived.

In the other 6 cases there had been no previous cesarean section. All were multiparas — 1 gravida VIII, 1 gravida IX, 1 gravida VI, 2 gravidas IV, and 1 gravida III. All had gone into labor at or near term. In 3 cases the rupture occurred after a few hours of labor, the diagnosis in 2 being obvious; in the other case the patient for a few hours was thought to have a premature separation of the placenta. All were treated by hysterectomy; all survived, but in all the infants were stillborn. In the other 3 cases the rupture was discovered subsequent to pelvic delivery of living children. In 1 case, with delivery by low forceps, there was no unusual bleeding and no shock, but after an hour

and a half the placenta still could not be expressed. When manual extraction was attempted it was found that the placenta had partly escaped from the uterus through a rupture of the lower segment. Immediate hysterectomy was done, and the patient survived. In the second case the patient had a precipitate delivery of an 8-pound infant and half an hour later went into severe shock. Vaginal examination then revealed a cervical tear, which extended into the lower segment. Immediate hysterectomy was followed by recovery. The third patient had a precipitate delivery of a 9-pound infant and sustained a severe cervical laceration, which was repaired. She developed peritonitis and died, and at autopsy it was discovered that she also had a rupture of the lower segment.

The following statement made in our previous report still applies:

> As a rule, when spontaneous rupture of the uterus occurs, the pain, the severe shock, the cessation of the fetal heart and sometimes the escape of the fetus into the abdominal cavity make the diagnosis easy. However, the pain may be very slight and may be obscured by labor pains, the bleeding may be negligible and shock absent, and the fetus may not escape through the rupture. Thus, it happens occasionally that when the abdomen is opened to perform a second section, a recent but entirely unsuspected rupture of the old scar is discovered. When such a symptomless rupture of the uterus occurs in a patient who is delivered vaginally, there is a grave abdominal emergency but little or no evidence of its existence. It may be diagnosed accidentally, as in a case . . . in which an extensive rupture of the lower segment just before normal delivery resulted in no change whatever in the patient's condition, and was discovered promptly only because the placenta escaped into the abdominal cavity; or such a rupture may be diagnosed only several days later when peritonitis has developed, or perhaps not until autopsy. Consequently, whenever a patient has been delivered vaginally who previously had a cesarean section, or whenever after vaginal delivery there is any reason whatsoever to suspect a rupture of the uterus, it is advisable to explore the uterus manually. In all cases of rupture of the uterus the best treatment is immediate supravaginal hysterectomy.

Fibroids

Fibroids are a common complication of pregnancy, and occasionally the interference with their blood supply as the uterus grows produces degeneration, pain, tenderness, slight fever and moderate leukocytosis. These symptoms are seldom very severe and usually subside with a few days of rest in bed. Since myomectomy is apt to be followed by miscarriage it is not advisable to undertake removal of the fibroids during pregnancy unless the symptoms are really severe and persistent.

In the ten-year period there were 6 cases of fibroids with symptoms that necessitated operation. In 5 there were the usual signs of acute degeneration, and a myomectomy was performed — 1 in the second month, 1 in the third, 1 in the fourth and 1 in the seventh. Four patients had uneventful recoveries, went to term and were delivered of living children. The fifth patient developed postoperative obstruction due to adhesion of the small intestine to the myomectomy wound. The bowel was freed at a second operation, and the patient recovered but a month later a macerated fetus was delivered. In the remaining case the symptoms from the fibroid were overshadowed by symptoms of acute intestinal obstruction. At operation a knuckle of bowel was found adherent to a markedly degenerated fibroid. The bowel was freed, the 5-month-pregnant uterus emptied by hysterotomy and then removed, and the patient made an uneventful recovery. This case is reported above in more detail under intestinal obstruction.

In addition there were 4 cases without acute symptoms in which operation was thought advisable. One patient at three months had a large pedunculated fibroid removed apparently for fear of torsion of the pedicle. She went to term and was delivered of a living child. One patient at six months was explored because of doubt whether the tumor was a fibroid or an ovarian cyst. A myomectomy was done and she miscarried fourteen hours later. One patient at five months had a cervical fibroid removed by vagina, went to term and was delivered of a living child. One patient, a gravida III, had a hysterectomy at four months because of multiple fibroids and very moderate pelvic pain. She made an uneventful recovery.

Summary

Any acute abdominal emergency may occur in a pregnant woman that can occur in a nonpregnant one, and the pregnancy itself presents certain additional hazards. The principles of recognizing and handling such conditions are the same in both groups. The prime necessity is not an immediate differential diagnosis but early recognition by the general practitioner or obstetrician that an acute abdominal emergency exists. He must maintain an attitude of suspicion regarding abdominal pain. Persistent pain is the one early and almost invariable symptom of an acute abdominal emergency, and demands immediate and careful consideration. He must take care that the existence of the pregnancy does not in any way distract his attention from the importance of abdominal pain or lull his suspicions. When these complications are promptly recognized and adequately treated, the danger both to the mother and to the fetus should be small.

THE ANTIHISTAMINIC DRUGS IN THE TREATMENT OF THE COMMON COLD*

A Study Conducted at Boston University

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BOSTON

A NUMBER of attempts have been made to determine whether various members of the antihistaminic group of drugs are effective in the treatment of the common cold. Among the studies reported to date, some appear to have demonstrated a beneficial or curative influence of one or more of these drugs in the common cold,[1-6] whereas others have failed to present any evidence that these drugs exert a favorable effect.[7-9] Until conclusive evidence is brought to bear on this problem, further attempts to determine the effect of the antihistaminic drugs on the common cold appear necessary.

The problem is beset by especially perplexing features: the common cold is a symptom complex without pathognomonic objectively recognizable features[10] and therefore readily confused by the patient and the physician with other conditions involving the respiratory tract (these include a number of virus and bacterial infections, vasomotor rhinitis, allergic conditions and, in the opinion of some, certain emotional states[11]); a wide variety of agents are claimed to be effective in the common cold, a fact that indicates not only that many are ineffective but also that a large element of suggestibility in both patient and physician is operating; those who sell the antihistaminic drugs have a very natural interest in having them used widely by the public, on the one hand, and on the other, it is perhaps not too far fetched to suggest that those who consider it their duty to protect the public from exploitation may be overeager to condemn the drugs.

METHODS

We have attempted to meet these difficulties, as others have, by proceeding in such a manner that no one having to do with dispensing the drugs would be in a position to know which of the antihistaminic agents were being investigated or the name of the company providing the drugs and financial support. Likewise, no information was given to anyone not directly involved with the running of the study concerning the presence or absence of a placebo. Notices announcing the study and calling for volunteers stated that free treatment for a cold was obtainable and that the purpose was to determine the effectiveness of the "new cold tablets" in the common cold. It was believed that the expectation of cure engendered by this announcement would bias the results equally for the placebo and the three drugs under study. The questionnaire used in this study included many more questions than the few believed to be required to determine whether or not there was an effect of the drugs on the cold. Certain questions were included so as to provide more than one way of obtaining the same kind of information. Finally, it was hoped that some advantage would be gained by "burying," in some degree, the key questions in the bulk of the questionnaire. We anticipated that some parts of the questionnaire would turn out to be superfluous.

A room on the ground floor of one of the main buildings of Boston University was used as a dispensary. This was open from 9:00 a.m. to 4:30 p.m. on weekdays and from 9:00 a.m. to 12:00 noon on Saturdays and was staffed by two assistants. The nature and the objectives of the study were fully explained to the assistants, but no indication of the identity of the three antihistaminic drugs was given them. They were told, however, that one of the four preparations to be used was a placebo, and they kept this in confidence. It is interesting that they failed to identify the placebo in the course of the study.

All persons connected with the University were eligible to volunteer. Upon arrival, each subject received the first questionnaire and filled it out at once. After checking the questionnaire to make sure that it had been filled out according to the instructions, one of the assistants gave the subject an envelope containing thirteen tablets of one of the four preparations under study. These were given out in rotation. Instructions were printed on the envelope as follows:

> Directions: — Take two pills as soon as you receive them and then take one every four hours. A convenient schedule is as follows: take one before breakfast, one before lunch, one before the evening meal, and one before bedtime.
>
> Caution: — If these pills make you drowsy, do not drive your car or engage in similar activities requiring skill.

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An appointment was made to return four days later. The drugs were packaged by the assistants, who filled the envelope from large bottles with a label indicating the number but not the name of the drug. Only one drug was packaged at a time so as to avoid errors in filling the envelopes. After the study was completed, sample packages were assayed chemically, and the quantity and type of drug were found to be correct. The drugs included in this study were the following:

Preparation 1 — prophenpyridamine (Trimeton), 10 mg.
Preparation 2 — pyranisamine maleate (Neoantergan), 25 mg.
Preparation 3 — placebo (lactose)
Preparation 4 — thonzylamine hydrochloride (Neohetramine), 25 mg.

Their appearance was identical, but there was a distinct difference in the taste of the four preparations. However, the comments concerning this were so few as to indicate that the difference in taste played very little part in the evaluation of the drugs used. The contents of the envelope were identified by a code on its face. Although this was noticed casually by a few of the volunteers, there appeared to be no appreciation of the significance of the code. Upon returning on the fourth day, the subject filled out the second part of the questionnaire. When completed according to instructions, the second part was stapled to the first and filed. A card file was also kept so that subjects returning for a second course of treatment for the same or a subsequent cold could be identified. Examination of the nose and throat was not done, nor did it seem warranted in a study of this size because of the difficulty in carrying it out on such a large scale and because the reliability of such an examination in the diagnosis of the common cold is open to serious question.[10]

Results

The study was begun on January 19 and continued to April 18, 1950. A total of 1214 subjects participated. There were 46 of these from whom no report on the effect of the pills could be obtained.

A tally was kept during the study of the answers to certain key questions in both parts of the questionnaire. Examination of over 1000 questionnaires by this means failed to provide any evidence that the three antihistaminic drugs under study had any effect differing from that produced by the placebo.

Because this means of study was of necessity limited, the data in the completed questionnaires were transferred to International Business Machine cards, which lend themselves to more elaborate analysis. After the questionnaires deemed invalid for a number of reasons had been discarded, those remaining totaled 729. The frequencies for each item in these questionnaires were tabulated. Table 1, which shows the responses to one of the key questions, is representative of the data obtained. The chi-square method of statistical analysis was applied to this group, and in no case was statistically significant evidence obtained that the effect of any of the three antihistaminic drugs under study differed significantly from that produced by the placebo.

The group of 729 questionnaires was rendered relatively homogeneous by the elimination of subjects with the following characteristics: a stated age of more than thirty-four or less than seventeen; failure of the volunteer to complete the follow-up questionnaire within eight days; the presence of a "cold" for more than three days; and subjects failing to take 6 or more of the pills given them. This reduced the group to 419. A second smaller group of 175 questionnaires was made up of those in which it was stated that one or more of any of the following were present: a watery or colorless nasal discharge, increased nasal discharge or obstruction and increased sniffling or nose-blowing. These two groups were analyzed in the manner described above. Again, no statistical evidence could be obtained that the effect of the antihistaminic drugs differed significantly from that of the placebo.

The elapsed time between the onset of cold symptoms and the administration of the first dose of one of the preparations was studied in the group of 419 for the effect on the course of the cold. The responses were grouped with respect to duration

Table 1. *Answers to Questions Regarding Effect of Drug.*

Preparation	No. of Volunteers	Effect on Course of "Cold"				
		Subjects who became worse	Subjects who remained the same	Subjects who improved slightly	Subjects who improved markedly	Subjects whose colds disappeared completely
Trimeton	184	37	29	39	53	26
Neoantergan	184	42	27	47	53	15
Placebo	177	46	20	33	56	22
Neohetramine	184	38	34	44	49	19
Totals	729	163	110	163	211	82

of symptoms: less than six hours; seven to twelve hours; and one day. Here, again, there was no effect of the three drugs that could be distinguished from that of the placebo.

Finally, as judged by the appearance of the new symptoms in the group of 729 volunteers *after* administration of the four preparations was begun there appeared to be, in general, some evidence that the incidence of "side-effects" was greater than that in those receiving placebos. However, the frequency of appearance of most of these effects was so small as not to permit valid statistical tests of significance. Accordingly, the nine symptoms with the highest frequency of occurrence were arbitrarily selected for examination. These, in order of frequency, were as follows: drowsiness, headache, dizziness, cough, weakness, running nose, stuffy nose, blocked nose and feverishness. With the exception of cough and running nose, the occurrence of these symptoms among the volunteers receiving the placebo was less than that among those receiving any one of the antihistaminic drugs. Though the result suggests that the three drugs were producing "side-effects" and perhaps even contributing to the symptoms of a cold, when the data were subjected to test no one of the differences was sufficiently large to take on statistical significance.

Summary

Between January 19 and April 18, 1950, 1214 subjects were given one of four antihistaminic preparations as treatment for the common cold. These were, in the order in which they were dispensed; prophenpyridamine (Trimeton), pyranisamine maleate (Neoantergan), a placebo (lactose) and thonzylamine hydrochloride (Neohetramine). Information obtained by questionnaire was tabulated on International Business Machine cards and subjected to statistical analysis. We were unable to distinguish any effect of the three drugs, in the dosage used, on the common cold that differed significantly from the placebo.

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THE NEED FOR PSYCHIATRY IN A MUNICIPAL GENERAL HOSPITAL

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AT THE Boston City Hospital, psychiatry labeled as such does not officially exist. Actually, about 1000 obviously psychotic patients are admitted to its wards each year. Most of these patients are also suffering from medical and surgical diseases. The hospital, furthermore, contains the usual large number of patients with psychoneuroses or psychosomatic disorders. This number has been variously estimated as 50 to 80 per cent of all admissions. Emotional disorders may be the main reasons for the admission of many patients, or they may constitute a burdensome complication in addition to whatever medical diseases affect them. The obviously psychotic patients are seen in consultation routinely by the house officers and the resident on the Neurological Service. Among these are many people over sixty years of age with senile psychoses. If they are found by special examining physicians to be committable they are transferred to the Boston State Hospital for further observation or treatment and custodial care. The countless cases of psychoneuroses are by necessity neglected for the most part for the following reasons: confusion of all psychiatric problems with the idea of "insanity"; actual lack of space, funds, equipment and personnel to cope with such a large problem at the present time (which is nothing new, since it has been that way for twenty-five years or more); lack of any definite plan to meet the situation; and failure to recognize the fact that there are large numbers of psychotic patients, including many sick old people, who need hospitalization for their medical or surgical problems as well as for their psychoses.

At one time or another an effort to improve or remedy this situation has been made, usually by members of the Neurological Service, which up to now has assumed responsibility for whatever care these patients have been given. But these efforts have proved inadequate to effect much change, and the basic problems have continued to exist, altered only by increasing needs as World War II and the postwar period have added new demands and have thrown increasing strain on the facilities of the hospital.

The annual reports of the chiefs of the Neurological Service have repeatedly emphasized the hospital's need for a psychiatric department that could supply at least elementary care for patients who might be helped by psychotherapy or some form of psychiatric care or guidance. For years members of the staff of the Neurological Unit have been sympathetic to the idea of making certain psychiatric services available to the patients of the Boston City Hospital, and several trustees, in the past, have expressed themselves as being strongly in favor and earnestly desirous of getting such work started.

At the present time it is possible that the physical difficulties are a greater obstacle than prejudice against psychiatry because just now there actually is no space, money, personnel or equipment available for psychiatric use and no immediate prospect of getting any. Every square foot of hospital floor space is needed for some special purpose. Every man-hour of available energy, trained or untrained, is allotted to some particular job, and even today the number of patients with severe disorders appears to be increasing as the cost of living rises. But it is also generally believed by those who are interested in this subject that, whereas the present is not a good time to try to expand psychiatry, it is nevertheless a good time to try not to lose whatever progress has been made in the past.

Those who have been resistant to the idea of officially recognizing psychiatry at the Boston City Hospital have presented the argument routinely that psychiatry is not wanted in the Hospital, and if patients need psychiatric treatment they may go to the Psychopathic Hospital or the State Hospital; "crazy" patients are not wanted here. This attitude has been restated with various formulas. Gradually these objections have been met in part by educating leaders to the point where it can be plainly seen that all patients in need of psychiatric treatment are not necessarily "crazy" and that all psychotic patients are not necessarily otherwise physically healthy. Most psychiatric patients, in fact, are not "crazy" — and the number of nonpsychotic patients in need of psychiatric treatment seems to be increasing each year. The point is that there are already hundreds of psychiatric problems in the wards of the Boston City Hospital that are not being adequately cared for. Also, the need for psychiatric care is so great and so widely accepted in medicine generally today that it can no longer be denied if a realistic attitude to medicine and human illness in general is adopted.

In view of all these difficulties it has been generally admitted that no separate department of psychiatry at the Boston City Hospital can possibly be founded or would be practical at the present time — lack of ward space, nurses, medical staff and money to support psychiatric work makes this impossible now. Since there is some space available in the outpatient building on weekday afternoons, since it is more practical to give psychotherapy to outpatients than to hospitalized patients and since

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a few physicians can be found who are willing to volunteer their services in limited amount as a contribution to the welfare of the deserving poor or marginally situated economic group of residents of Boston, it appears that the most economical and the most practical way of beginning psychiatric work at the Boston City Hospital would be to develop an outpatient psychiatric clinic.

The staff of the Boston City Hospital has been definitely co-operative in approval of this plan, particularly the members of the teaching services. For some time it has been recognized that the development of a psychiatric outpatient service would be of distinct benefit to the hospital as a whole and especially to the medical and neurologic outpatient clinics, from which many patients are referred for psychiatric consultation and treatment.

But the problem of gaining official approval still remains, and once that hurdle is passed there will still be the problem of finding trained personnel, money, space, time and assistants with energy, interest and proper training to carry on such a project once it were started. Such progress is not an impossibility, but it is far from an easy achievement even though the need for the facilities continues to exist and to grow. So it is that those who are interested in seeing psychiatry develop at the Boston City Hospital view with pride each new advance in the field of psychiatric work in other Boston hospitals and continue to look forward to the day when outpatient psychiatric treatment will be available to the citizens of Boston in their municipal hospital system as it is in all the other large privately supported hospitals of this city.

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FIFTY YEARS OF MEDICAL PROGRESS

MEDICINE AS A SCIENCE: PHARMACOLOGY*

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AT THE turn of this century the medical profession had entered into a period of therapeutic nihilism, at least so far as its leaders were concerned. The teachings of Weir Mitchell[1] had laid emphasis upon the therapeutic efficacy of faith, rest, fresh air and pure water. The cardinal principle of therapeutics, *primum non nocere* (in free translation, "it is better to let the patient die than to kill him"), had been re-enforced in the dominant thinking of the day by a growing distrust of the old materia medica. Indeed, Oliver Wendell Holmes had stated, in his inimitable way, "If the whole Materia Medica (excepting only opium and ether), as now used, could be sunk to the bottom of the sea, it would be all the better for mankind, — and all the worse for the fishes."[2] To be sure, the local physician was still dispensing those universal remedies calomel, castor oil and sweet spirits of niter, but an increasing mass of laymen was beginning to consult the "diagnostician" and learning from him a profound disbelief in the efficacy of medicines, which often were closer to placebos than palliatives.

As for specific drugs, they were few and far between, and the lack of adequate control by the clinical laboratory, combined with poor standardization of the drug preparations, interfered considerably with the net effectiveness of these often toxic drugs.

Part and parcel of this lapse in therapeutic progress was an apathetic attitude among pharmacologists, which amounted to frank decadence. Originally the outstanding continental pharmacologists had been men with a lively interest in human disease and in chemistry. During the nineteenth century they were the heirs of the iatrochemical school of Joseph Priestley and John Mayo. They included such men as Claude Bernard, who although a brilliant experimentalist, never forgot that he was a physician. At the dawn of the twentieth century, however, experimental pharmacology had fallen into the hands of physiologists, who in their ivory towers (with notable exceptions) were content to devise ingenious experiments with lower forms of life under circumstances that had no relevance to human disease. While pharmacology floundered in the doldrums of gross mammalian physiology, the advances in treatment were being made by the rising school of clinical investigators, typified by Meltzer and the young men whom he inspired.

As Welch and Bueding[3] have stated:

> In general, pharmacologists must face the indictment of having viewed with too great complacency the limitations of the classical physiological attack upon the basic mechanisms of drug action. The continued emphasis upon the physiological approach led to many improvements in our understanding of the action and proper usage of important therapeutic agents, but, during recent years at least, such methods have rarely opened new fields of research.

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A generation ago, even though some universities maintained departments of "pharmacology and *experimental therapeutics*," these were rarely consulted by clinical colleagues, who had ceased to receive from them advice that applied to the clinic. Medical students began to yawn and even groan during their courses in pharmacology. As matters went from bad to worse, vigilant and economically minded deans found it convenient to tuck a pharmacologist into the roster of the physiology or biochemical department.

The Renaissance of American Pharmacology

In the midst of this neo-medieval stage of the specialty, three great features preserved the life of modern pharmacology, which is indeed the youngest of the preclinical sciences. The first of these forces, which tided pharmacology over its infancy, was the brilliant work of a few distinguished scholars like Abel, Clark and Hans Horst Meyer, discussed below in greater detail. The second factor, which preserved pharmacology as a potent influence in medical progress, was the timely rise of biochemistry, — stemming from Chittenden, of Yale, whose pupils founded departments in medical schools all over the country and trained a considerable number of future clinical investigators. Indeed, toward the end of World War I, practitioners of medicine came to inquire satirically, "Which biochemist will be made the new professor of medicine?" This movement, however, gave a considerable impetus to the development of rational therapeutics because it led to the development and use of clinical chemistry, not only for diagnosis but also for therapeutic guidance. It also instilled new blood into pharmacology proper. For instance, it can be maintained that the discovery of insulin would have been impossible without an extensive background in the measurement of blood sugar. Although, strictly speaking, this discovery did not arise in a department of pharmacology, it affords a good example of what might have been accomplished had departments of pharmacology been organized appropriately in 1921.

Industrial Research Institutes

The third factor, which led to great advances in pharmacology proper, was the development of progressive research institutes in association with pharmaceutical industry. In Europe such institutes had appeared in the last century in close co-operation with the universities. Indeed, even today the director of a large continental industrial research institute may hold simultaneously the chair of pharmacology in the local university. This sort of arrangement has been frowned upon in Anglo-Saxon tradition, but the holier-than-thou attitude has greatly handicapped American departments of pharmacology. In the meantime some of the outstanding advances in pure science, like the isolation of vitamin B_1 and vitamin B_{12}, have come from industrial research institutes, with their manifold resources and equipment. One healthy corollary of this development has been an increasing interchange of personnel between universities and industry (in both directions).

It is impossible to estimate the contributions made to pure science by the large industrial research staffs in the United States during this century. Headed by men of professional caliber (for example, Chen, of Eli Lilly, Molitor, of Merck, and Tainter, of Sterling–Winthrop) these organizations have played an increasingly important role in the advancement of basic knowledge. One wishes that one could name them all! In general, however, the detachment of several of these institutes from the production departments proper has facilitated greatly the development of new types of drugs. The brochure *The Next Half Century In Medicine*, recording a symposium held at the dedicatory exercises of the new Sterling–Winthrop Research Institute, holds many interesting suggestions for future trends in science.[4] Some of these are quoted below.

Graduate Education

Only a little over a decade ago one frequently heard the question, "Why have pharmacologists not reproduced themselves?" Indeed, at a conference on graduate education in pharmacology held at Yale in January, 1947 (under the auspices of the American Society for Pharmacology and Experimental Therapeutics), it appeared that over a five-year period there would be available nearly 500 positions in the United States and only 200 trained applicants. Probably there are now some twelve university departments in this country with well organized programs for graduate training. These are to be distinguished from the desultory training of an occasional fellow who drifts into the pharmacology department from a cognate field or from medicine proper.

Clinical Pharmacology

University deans and faculty boards are slowly becoming aware of the need for organized teaching in clinical pharmacology. This trend is manifest in regular therapeutic conferences, such as those held at Cornell and Yale, with participation by both pharmacologists and clinical specialists. Outstanding among such associations has been the Cornell team of Cattell and Gold.[5] The nineteenth-century concept of a professor of therapeutics is slowly returning in a modified form, consonant with the development of a potent materia medica based upon the sound mechanistic tenets of rational (rather than empirical) therapy. Such an advance is dependent upon the clear vision of the professors of medicine and surgery, who can readily obstruct progress of this sort if (for one reason or another)

they maintain a medical monopoly of their (*sic!*) "clinical material." Obviously, the joint appointment has gone far to facilitate such an arrangement in several outstanding instances.

Anesthesiology

Some of the most interesting human pharmacology is now published by the official organ of a new group of specialists.[6, 7] Anesthesia as a full-time medical specialty has made great strides in the last two decades. Modern clinics are developing sections on anesthesia, with a score of interns or residents under advanced training. This new specialty grew out of pioneer studies like those of Seevers and Waters, Barbour and Bourne, Leake and Hathaway, Schmidt and Dripps and Krantz and White. This application of fundamental knowledge to clinical problems has frequently expressed itself in such fruitful collaboration between preclinical scientists and clinicians. Among other universities, Pennsylvania and Harvard have been especially farsighted in supporting a professor of anesthesiology with close association to pharmacology. Nowadays, medical anesthetists trained under the new dispensation are keenly aware of the advantages of adequate preoperative and postoperative care. Less often will it be said that the operation was successful, but the patient died.

Outstanding Leaders in Pharmacology

Man is naturally a hero-worshiper, and it is tempting to believe that science progresses through the brilliant broken-field running of individual geniuses. In every generation it is easy to nominate a few outstanding persons as "the most distinguished pharmacologists of these times." In 1899 one would immediately have thought of Schmiedeberg, Bernard and Hans Horst Meyer. In 1950, as one surveys the past half-century, a panorama of names and personages comes to mind: Abel, Cushny, Clark, Hunt, Voegtlin, Loevenhart, Dale, Loewi, Wallace and several others. It would be tempting to give a biographic sketch of each of these outstanding scientists, but for the moment perhaps the discussion had best be limited to Abel. The American Society for Pharmacology and Experimental Therapeutics offers an annual prize in his honor, and, in presenting one such award, Geiling[8] has given a masterly picture of the man. From this survey an important fact stands out — namely, that Abel dared to venture outside the classical fences of his field. In particular, in a day when endocrinology was generally considered as near-quackery, Abel did brilliant pioneer research on epinephrine, posterior pituitary extract and insulin. This does not mean that he was unacquainted with the broad background of his profession but rather that he was not hidebound by it.

As Geiling has emphasized, the beginning of this half-century saw the establishment of a number of chairs of pharmacology in the United States. This recognition of pharmacology as an autonomous science was based on the prestige of certain European departments, and especially that of the Schmiedeberg "school" at Strasbourg. Among eminent American leaders, Abel, Cushny, Wallace, Richards and Sollman all spent some time with Schmiedeberg; indeed, Abel took his degrees at Strasbourg before he went to Michigan, and Cushny followed in his footsteps. After Abel went to Baltimore, his department became a center for the training of leaders in the specialty, and men like Reid Hunt, who had contact with Abel, later filled the newly established professorships. Dr. R. P. Walton has informed me that there was no operating pharmacology laboratory in the South before 1900. One was established by Dr. W. deB. MacNider in North Carolina in 1905, and one by Dr. P. W. Rowland in Mississippi in 1907. This professorial group consisted of experimentalists, who tended to minimize the old-time, dull teaching of the materia medica. Other laboratory chiefs followed suit, notably Edmunds at Michigan, A. N. Richards at Philadelphia, and Barbour and Underhill at Illinois (later at Yale). Abel's[9] own account of his invitation to Michigan, received at Bern while he was working with von Nencki, is illuminating, and particularly von Nencki's advice (about September, 1899) to the younger man: "Here is an opening for you in your native land, and while you have not especially planned to enter the field of Pharmacology I can tell you from my knowledge of the subject that it is one of the broadest fields in medicine, . . . one that can be approached from many points of view and one that can afford an opportunity for research work of many types, in accordance with the previous training and ability and originality of the man who elects to work in this field."

Abel began work at Ann Arbor early in January, 1890. He says:

> After a few medical consultations and the taking over my old friend Herdman's practice for ten days while he was away on a vacation, I decided that it was impossible to serve two masters, and so dropped all ideas of carrying on internal medicine and devoted myself entirely to my subject. Here at Ann Arbor I was given the opportunity of starting the first professorship of pharmacology in the United States, whose holder should devote himself entirely to giving students the best possible instruction by means of lectures, demonstrations and quizzes, in the manner in which my European teachers (Schmiedeberg and Boehm) had long carried on their work. All my energy that was not given to this kind of instruction to students was devoted to research work and to arousing the enthusiasm of others for it.

This was the first full-time university professorship of pharmacology in the United States. Until 1890, the subject had been taught by medical practitioners. Although Cushny's laboratory at Ann Arbor was probably the first outstanding department in the country, Abel is generally regarded as being the father of American pharmacology. In part, this is because he started the American So-

ciety for Pharmacology and Experimental Therapeutics in 1908 and founded the *Journal of Pharmacology* shortly thereafter.

After two years at Michigan, Abel established the Pharmacology Department at Johns Hopkins University, where he remained until his death in 1938. With Herter he founded the *Journal of Biological Chemistry* in 1905 but transferred his allegiance in 1909 to the *Journal of Pharmacology and Experimental Therapeutics*, which he edited for twenty-three years.

It might almost be said that the history of pharmacology in the United States up to 1935 is chiefly the story of Abel's researches and those of his pupils. It is frankly impossible to review even in cursory fashion the lives and contributions of the many eminent scientists of the period under consideration. It may be interesting, however, to scan a list assembled at random by Professor Harvey B. Haag, for many years secretary of the Society (it should be noted that Professor Haag has deliberately not included the names of any active contemporaries):

In the United States worked:

Abel	Meltzer	Edmunds
Cushny	Underhill	Wallace
Hatcher	Barbour	Hirshfelder
Loevenhart	Hunt	Auer

Of those still living are:

Sollman	Jackson
Hanzlik	Lamson
Richards	Voegtlin
Tatum	MacNider

Of workers abroad during this period, one would think of:

Dixon	T. R. Frazer	Gottlieb
Trendelenburg	Fourneau	Heffter
Straub	Frankel	van Leeuwen

Of those living:

Loewi	Heymans
Clark	Pick
Burn	Trevan
Gaddum	Stoll

From Canada J. K. W. Ferguson, in commenting upon outstanding pharmacologists, has offered the following critique:

> The names which come to my mind first are, of course, Abel and Dale. After that, what I call the statistical revolution comes to mind, which dates in my mind from the article of Trevan on the error in the measurement of the lethal dose, in 1927, followed by Gaddum and greatly amplified by Bliss. Still on the intellectual front, I think of the intellectual nihilism of A. J. Clark and its important, though chilling, effect on our thinking. Turning to the chemical materialistic front, there is indeed a host of names, starting perhaps with Ehrlich, Fourneau, Stoll, Domagk, Florey and Fleming, Waksman, Henderson and Lucas, and Eddy. I cannot forget, either, the contributions of Reid Hunt, Sollman and Hanzlik, and Cushny, though it is hard to classify these.

What are the significant practical achievements of this half-century? Here are a few of them, suggested by K. K. Chen and J. C. Krantz, Jr.:

The establishment of pharmacology as a specialty in the United States when experimental methods were designed, pharmacologic societies formed, and pharmacologic journals published.

Abel's isolation of "adrenaline" in 1900, together with his studies on pituitary extracts (1919), and the crystallization of insulin (1926), which made endocrinology part of pharmacology.

The discovery of stimulants such as strychnine, and depressants such as morphine.

Houghton's standardization of digitalis (1900).

The work of Schmiedeberg on digitoxin, which led to the isolation of numerous other substances having a similar action.

Reid Hunt's work on acetylcholine (1906), which was followed by elaboration of the theory of the chemical transmission of nerve impulses.

The introduction of synthetic organic drugs in addition to natural alkaloids and glycosides, — including barbiturates, atropine substitutes, Atabrine (quinacrine), sulfonamides, and many new drugs for the relief of pain, spasm and nervous agitation.

Diagnosis by means of drugs — for example, phenolsulfonphthalein (about 1915).

Ehrlich's work on arsenicals, which marked the starting point of chemotherapy (1916).

The first generally used synthetic local antiseptic, Mercurochrome (1921) — even though this has now largely been supplanted.

Sympathomimetic amines beginning with work on ephedrine by Chen (1922).

Abel's work on an artificial kidney, which has recently been utilized in clinical medicine.

The description of drug metabolism by radiotracer technic since World War II.

The rise of anesthesiology, which freely borrows the knowledge of pharmacology.

The application of vitamins, antiseptics and chemotherapeutic agents — for example, the sulfonamides (1935) and antibiotics (Fleming, 1929, and Florey and Chain, 1939) — for the *prevention* of disease.

The tremendous expansion in knowledge of the steroid congeners including digitoxin, vitamin D, sex hormones, corticoids and carcinogens.

The systematic delineation of adrenergic and cholinergic drugs, and the discovery of inhibitors like D. F. P. (di-isopropyl fluorophosphate).

The studies of histamine (such as those conducted by Dragstedt) and of antihistaminics (such as those carried on by Fourneau and Bovet).

This list suggests that much has happened in the lifetime of many an elderly pharmacologist now alive. Indeed, if he reflects on the few dates given above, it will seem "only yesterday" that

several of these well established advances occurred. In a recent review, Sir Henry Dale[10] has said:

> Look back, those who can do so, to the beginning of this century, and recall again the state of medicinal treatment fifty years ago . . . We who have been able to watch the beginning of this great movement, i.e., therapeutics as an experimental science, may be glad and proud to have lived through such a time. . .

New Drugs

In retrospect, the basis for this resurgence in pharmacology has been the discovery of many new chemical substances with highly potent and specific actions. In the words of John Wycliffe,[11] "Trueth in the ende shall preuayle." As pharmacology waned in universities through academic shortsightedness, it sought new channels in clinical and industrial institutes. In the United States the advent of brilliant minds in the persons of displaced scientists has contributed signally to this rebirth. Moreover, pharmacology (including experimental therapeutics) is the natural repository of discoveries made under the aegis of cognate sciences. Each new vitamin, each new hormone and even each new enzyme is likely to swell the armamentarium that is tomorrow's materia medica. In this short essay, only a few of the outstanding discoveries that the pharmacologist now adopts as his own can be noted. Standing in mid-century, however, it is a little disconcerting to observe how many adopted children there are under the pharmacologic roof. In enumerating a few of these in the following pages, it will be a joy to find an occasional offspring that some brilliant pharmacologist can acknowledge as his own. Perhaps the reader will pardon me if these legitimate discoveries are given more consideration than the adopted ones.

To illustrate this point I prefer to hide behind the name of Otto Loewi, who kindly suggested the following list:

Hormones, starting with secretin (Bayliss and Starling); Adrenalin (T. R. Elliott) and its derivatives, thyroxine (and antithyroid drugs), sex hormones, ACTH and adrenocortical hormones.

Vitamins (and antivitamins).

Antibiotics, including the sulfonamides (Domagk and Woods).

Toxins — mode of action (H. H. Meyer).

Body constituents: acetylcholine (Dale), histamine (Dale and Richards) and antihistaminics (Bovet and Staub).

Substitutions such as Demeroi, purified curare and veratrine.

Dicumarol and heparin.

In general, one cannot help being impressed by the highly chemical flavor of this synopsis, and by the inappropriateness of cat, cannula and kymograph as means for studying many of these compounds.

Philosophic Considerations

More important, however, than the advances of individual men has been the march of ideas during these fifty years. To this progress many important contributions have been made by investigators not professing pharmacology.

Clinical and Biochemical Influence

A very important trend in the resurgence of modern pharmacology has been the instillation of biochemically trained members into its personnel. In part this transfusion has included experts in clinical metabolism, who often have unconsciously exerted pressure that assured the pertinence of experimental planning. Many an ivory-tower pharmacologist has resented the notion of pertinence, because he confused it with the term *applied* or *practical*. It goes without saying that pure research can make no progress if restricted to the engineer's point of view. It is even more true, on the other hand, that pure research may easily degenerate into a series of disconnected, albeit brilliantly ingenious, "Rube Goldberg" experiments, so that all philosophical direction and force is lost.

Drugs and Enzymes

This biochemical bias has directed pharmacologic thinking toward cell physiology — that is, fundamental pharmacology. One of the important prevailing philosophies of today is that "the site of drug action" involves the complicated interrelated enzymic reactions within the cell protoplasm. The old philosophy of Fontana (eighteenth century) that drugs act upon certain morphologic units (as anatomically defined) is going by the board, and many of the most fundamental pharmacologic phenomena are now being studied in terms of enzyme chemistry. For example, the action of physostigmine is always discussed together with cholinesterase. Not until recently have Riker and Wescoe[12] dared to suggest that it might have an action apart from this enzyme. This is no exception to the trend in enzymic thinking; rather, it simply indicates the recognition that physostigmine may influence an enzyme located within the cell as well as one located without. A whole series of important associations of enzymes with drugs is now in evidence, and only a few can be mentioned here. For example, Gaddum and Kwiatkowski[13] have suggested that ephedrine inhibits the action of an enzyme that otherwise would destroy rapidly the secretion of the adrenal medulla and its congeners. Similarly, the effect of narcotic drugs (including anesthetics) has been studied in terms of the suppression of oxidative processes within brain tissue. To this suppression of enzymic activity in chronic morphinism, Shideman and Seevers[14] observed a cellular reaction leading to an increased and sustained rate of oxidation. This compensatory hypertrophy, as it were, of intracellular enzyme

systems could explain the clinical state of agitation of the addict on sudden enforced abstinence.

Many of these enzymic studies in relation to drugs are still in the preliminary stage. The poisoning of cytochrome C by cyanide, however, constitutes an elaborately defined story,[15] which is amplified even further by the competitive action of methemoglobin as an antagonist. Moreover, in *comparative* pharmacology the presence or absence of a certain enzyme can explain why drugs act differently in different species. For example, the rabbit can eat "deadly nightshade" with impunity because that animal is equipped with enzymes that facilitate the inactivation of belladonna alkaloids. Similarly, Bass et al.[16] reported that ethanolamine produced methemoglobin in 2 workmen, although this drug had failed to do so in mice. Obviously, the human organism converts this substance to p-aminophenol, whereas no murine enzyme is available to effect this transformation. In this instance, the lack of an enzyme system was advantageous to the mouse.

The expanding field of antibiotics and of antiparasitic drugs is based upon such differential chemical affinities between host and invading organism. The object of modern chemotherapy is to inhibit essential enzymes in the parasite without seriously disabling the tissues of the host. In the case of the colon bacillus (*Escherichia coli*), nature long ago recognized the deadly nature of penicillin for certain bacterial metabolic processes and provided this little organism with an enzyme, penicillinase, that specifically destroys penicillin. Therefore colon infections in man do not yield to penicillin treatment. Without modern interest in enzymes the situation could not be interpreted.

It might well be said that the most important additions in this century to man's therapeutic armamentarium consist in vitamins and hormones. Even here the enzyme rears its hopeful head, because it begins to appear that these highly specific catalysts operate as constituent members of important intracellular enzyme systems. In so doing, they must follow a well defined quantitative pattern. For example, thyroxine is colloidally bound in the peripheral tissues. Too little of this "thyrenzyme"[17] results in a slowing of metabolism and in morphologic changes ultimately. On the contrary, if the tissues contain too much "thyrenzyme," tissue metabolism may be accelerated to the point of exhaustion and wasting. Indeed, the optimal concentration of many potent drugs is of the same order as that of the hydrogen ion. Quantitative control is essential, because an excess of a potent drug often leads to the so-called reversal of action. Thus, nicotine in low concentration is excitant whereas higher concentrations paralyze.

Quantitative Pharmacology

Quite distinct from factual learning have been two ancillary movements, which have served greatly to reinforce and buttress the profession in this century. In a sense, both these movements grew out of the "general or fundamental pharmacology" as expounded by Clark.[18] His careful studies of fundamental relations between dose and effect, and of the basic relations between time and concentration, led to investigations of drug action at the cellular level. Perhaps such was the dream of Buchheim a century earlier! At any rate in the first place theoretical quantitative pharmacology has developed apace, so that, for instance, I have felt no hesitation in formulating nomograms describing the action of thyroxine and of digitoxin, respectively. Indeed, the best trained young pharmacologists today are equipped with a systematic background in two important features of biometrics — namely, optimal experimental design and bioassay in its application to manifold types of drugs. So important has this aspect of the field become that Wills[19] recently devoted a considerable portion of an article to dose-effect relations and similar mathematical functions.

Secondly, in the application of this quantitative trend has come a better organization of the official compendia. Without minimizing the achievement of Harvey Wiley in 1906, the new Food, Drug and Cosmetic Act of 1938 (with its new-drug section) gave a tremendous impulse to professional pharmacology. More than ever before, pharmacologic data of considerable exactitude are obtained routinely for prospective therapeutic agents. Since the advent of meperidine (Demerol), the older pharmaceutical approach of modifying known, natural substances has given ground to the possibility of developing *de novo* synthetic drugs for various purposes. In such work the necessity for discriminating quantitative appraisal has become increasingly apparent. This methodology has been applied extensively for the government agencies by the late Herbert Calvery (originally a biochemist) and by Erwin Nelson in the control of medicinals, and by Nathan B. Eddy and Himmelsbach in the study of narcotics. The recent reorganization of the *United States Pharmacopoeia* on a representative basis, with electors delegated from literally hundreds of universities and learned societies or institutions, has served to implement the application of quantitative, applied pharmacology for the benefit of the public. In this work the Council of Pharmacy and Chemistry of the American Medical Association has ably participated.

Crystallization of the Field Called Pharmacology

The past generation has been a period of searching self-examination for many members of the relatively new profession, who more than once have asked themselves "What is pharmacology?" In this connection the statement by Otto Loewi[4] is pertinent:

Pharmacology, my profession and at the same time my hobby for more than fifty years, is an autonomous branch of biology aiming at the exploration of organic structures and functions through the study of their changes as produced by chemical agents. Pharmacology is also a medical science, for many chemicals (the so-called drugs) have played an important part in the therapy of disturbed functions. One could roughly divide pharmacological research into two groups: the first includes the study of the final effects, the second the study of the basic mode of action of chemicals, including drugs.

As Leake has pointed out, pharmacology has not yet achieved such a state of logical consistency that broad scientific generalizations or laws can be made. It is still in the maturation stage. Out of Ehrlich's concept of "chemotherapy," however, has developed the widespread recognition of Clark's "general or cellular pharmacology." His application of the methods of quantitative pharmacology led to a study of the mechanisms of drug action on a cellular level. This involves the appreciation of enzyme chemistry and the principle of competition between related compounds for metabolic energy. Indeed, the distinction between competitive and noncompetitive inhibition is of relatively recent origin.

In commenting upon this nebulous state, Rene J. Dubos[4] has said:

Whereas immunology appears to be developing according to a clear inner logic, the growth of chemotherapy has been (so far) governed almost exclusively by chance. Practically all useful drugs have been discovered as a result of accidental observations or of empirical search by trial and error . . . Nevertheless, it must be admitted that despite the lack of a theoretical basis to chemotherapeutic research, new drugs have been discovered at an ever-increasing rate during the past few decades. When the century opened, a few antimicrobial drugs of natural origin (particularly quinine and emetine) were available, and Ehrlich was just beginning his tests with dyes and arsenicals. In addition to Salvarsan, only a few other synthetic compounds, most of them effective against protozoan infections, were introduced into medical practice between 1900 and 1935. In contrast, the sulfonamides and penicillin heralded an era which saw the discovery of entirely new types of natural and synthetic drugs and gave rise to the faith that all infective diseases would eventually be found amenable to chemotherapeutic treatment . . . The concept of antimetabolites provides a theory for the synthesis of an endless variety of compounds capable of interfering with growth by competing with normal metabolites in certain reactions essential to living processes . . . During the past few decades, emphasis in the treatment of infection has been placed on the use of more or less specific agents capable of interrupting microbial multiplication *in vivo*.

The Current Trend

Szent-Györgyi's[5] recent comment on biochemistry might well have been said of pharmacology:

We know nothing . . . about the dimension below 1000 Angströms. . . So I can tell you in one single sentence what I expect from biochemistry as its main contribution during the second half of this century. The first half we have spent in isolating active substances. The second half will be spent in explaining how they act — by *penetrating into the structure and organization of living matter*, giving herewith to medicine the foundation it needs to be elevated into the status of a science . . . The future is the continuation of the past, the present being the dividing line between the two. If we want to see ahead we must look back.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

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CASE 37041

PRESENTATION OF CASE

A sixty-three-year-old man was admitted to the hospital because of a productive cough and hemoptysis.

Six months prior to admission he was sent home from work by the plant physician because of chills and fever of "over 100." He remained at home in bed for two weeks with fatigue, achiness and fever. Four months before admission he noted the gradual onset of a cough that was productive of yellow foul-smelling mucus. This was not associated with fever, chest pain or dyspnea. Beginning one month prior to admission he coughed up as much as a cupful of bright red blood every two to three days. During the present illness he had noted increasing fatigue and a sensation of "heaviness" and wheezing of the left chest.

The past history was noncontributory. There was no history of tuberculosis. The patient had consumed three to four quarts of beer, or one or two quarts of wine, "all his life," and had smoked one or two packages of cigarettes daily for many years. He had had an estimated weight loss of fifteen pounds in the last two years, and five pounds' weight loss in the last six months.

Physical examination revealed a rhinophymatous, slightly dyspneic man with slight cyanosis of the lips. There was a foul odor to his breath. Examination of the lungs showed dullness, decreased breath sounds, tactile fremitus and voice sounds at the left base with scattered rhonchi. There was a Grade III to IV systolic murmur at the base of the precordium that obscured the aortic and pulmonic second sounds and was transmitted to the neck. The liver was felt one fingerbreadth below the right costal margin by one observer and three fingerbreadths below by another.

The temperature was 102°F., the pulse 80 and the respirations 25. The blood pressure was 110 systolic and 70 diastolic.

Urinalysis and determinations of the chemical contents of the blood were within normal limits. Examination of the blood disclosed a hemoglobin of 9.1 gm. per 100 cc., a red-cell count of 3,520,000 and a white-cell count of 22,100, with 81 per cent neutrophils. X-ray examination of the chest showed that the left leaf of the diaphragm was somewhat elevated and that its motion was limited. Probably both fluid and thickened pleura obscured the lateral portion of the left leaf of the diaphragm. Within the left lower lobe, which was somewhat reduced in size, there were two cavities, the larger

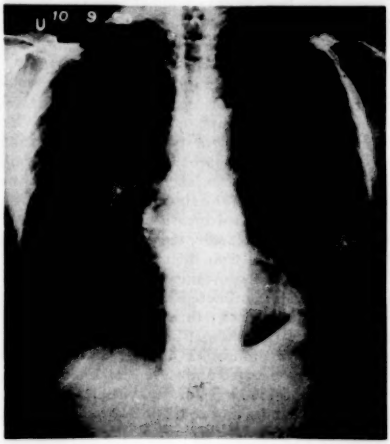

FIGURE 1. *X-ray Film of Chest. Arrow points to cavity.*

of which was at least 3 cm. in diameter (Fig. 1). These cavities lay posteriorly and were probably within the subsuperior or posterior basal segment. The lungs elsewhere appeared clear. There was probably enlargement of the interlobar bronchial lymph nodes. The left lower-lobe bronchus, however, could not be traced much beyond its origin in any of the views. The heart, aorta, and bones were not remarkable.

Bronchoscopy by one observer showed no definite evidence of tumor, but because of severe coughing and bleeding it was felt that a repeated examination was indicated. A second bronchoscopy showed, within 1 cm. of the carina, an area of fixation and narrowing on the medial wall of the left main bronchus, which extended downward for several centimeters and became increasingly narrowed, with more nodularity and more fixation. The left

upper-lobe orifice could not be seen, because of nodularity and narrowing. A satisfactory biopsy specimen obtained with a cutting forceps was reported as showing acute and chronic inflammation with scarring. A smear of the secretions aspirated for cytologic study was reported as unsatisfactory.

The hospital course was uneventful, and on the thirteenth hospital day an operation was performed.

Differential Diagnosis

Dr. Donald S. King*: It is interesting that the patient had a productive cough, but there is no indication that the sputum was examined.

Dr. Benjamin Castleman: Four sputum examinations were all negative for acid-fast bacilli. They were cultured and showed alpha-hemolytic streptococcus, *Staphylococcus aureus* and *catarrhalis*.

Dr. King: Such a report is of course important.

At first glance this certainly seems to be the picture of bronchogenic carcinoma with metastases to the mediastinal lymph nodes and pleura. The history is consistent with pulmonary suppuration beyond an obstructing bronchial tumor. The foul sputum could come from such an abscess and the large hemoptysis from the abscess cavity. The physical signs — diminished breath sounds with a localized wheeze on the left side, the anemia and the high white count — are consistent with bronchogenic carcinoma with suppuration. The bronchoscopy showed several centimeters of nodularity, with narrowing and fixation; this finding to me spells cancer. The x-ray films also showed that the left lower lobe was diminished in size and that the diaphragm was elevated and its motion limited. The bronchus to this lobe was not well visualized. There were pleural changes that could be due to metastases, possibly some fluid and a cavity that could be an abscess cavity. So this seems to me a fairly clear-cut story of carcinoma of the bronchus.

But what is lacking in the picture? The sputum was not examined for tumor cells, and the bronchoscopic biopsy that showed acute and chronic inflammation does not help me very much. The material from the bronchoscopic aspiration was negative for tumor cells. It does not rule out carcinoma, by any means, but it makes me wonder if I am dealing with an unusual type of infection.

In the x-ray films the cavity in the left lower lobe looks like a cavity that one sees with chronic infection. My question here would be: Is there evidence that would add anything to the original diagnosis of bronchogenic carcinoma? For instance, could this be a tuberculous cavity?

Dr. James J. McCort: It is a thin-walled cavity, such as is more commonly seen secondary to bronchial obstruction. The lack of calcification in it or around it is against tuberculosis.

*Member, Board of Consultation; formerly, physician, Massachusetts General Hospital.

Dr. King: The lack of calcification is perhaps against tuberculosis, but it does not rule it out.

Dr. McCort: It would mean that a chronic tuberculous process is unlikely. Another smaller radiolucent area lies below the one you have indicated, and it may also represent a small abscess cavity. The greater portion of the disease is seen posteriorly. It involves the posterior basilar segment and extends up into the area that is defined as the subsuperior segment. The latter may exist as an independent segment.

Dr. King: So you have in your terminology a superior and a subsuperior?

Dr. McCort: Boyden and his co-workers[1, 2] have found a subsuperior zone in 100 per cent of 60 specimens of the right lower lobe and 100 per cent of 50 specimens of the left lower lobe. It is interpolated between the superior and basal segments on the costal surface of the lobe. The name is derived from the fact that an independent dorsal ramus arises from the stem bronchus just below the superior segment bronchus in 29 per cent of cases on the left side and 62 per cent of cases on the right side.

Dr. King: The history read "interlobar bronchial lymph nodes." That is an x-ray expression isn't it?

Dr. McCort: No; the term is taken from Rouvière.[3] He divides the lymph nodes concerned with drainage of the lungs into four major groups: anterior mediastinal or prevascular, peritracheobronchial, intrapulmonary and posterior mediastinal. The interlobar lymph nodes are part of the intrapulmonary group. These interlobar lymph nodes lie in apposition at the bifurcation of the main artery and bronchus to each lung. In the adult the nodes are surrounded by lung and pleura, although in origin they are thought by Rouvière to be extrapulmonary. In this patient the interlobar nodes on both sides are seen to be enlarged.

Dr. King: The heart is not displaced to the left. Would you have expected it to be, with that much atelectasis?

Dr. McCort: The heart is slightly to the left. There is some reduction in size of the left lower lobe.

Dr. King: I still wonder about tuberculosis or some other chronic infection, but I shall have to assume that everything can be explained on the basis of carcinoma with secondary infection.

There are two other features that come into the picture. First: A murmur was present, which obscured both the pulmonic and aortic second sounds and was transmitted to the neck. I do not see how aortic stenosis could account for these signs. I should think that pressure from malignant lymph nodes along the vessels might have caused them. I do not know how to explain them on the basis of intracardiac disease. Secondly: The liver was enlarged significantly, but I do not believe the enlargement

was caused by portal cirrhosis that leads to blood spitting, so I shall forget it. I shall say that this was a case of bronchogenic carcinoma with metastases to the mediastinum and probably to the pleura. Do you think the pleura may have been involved, Dr. McCort?

DR. MCCORT: It is very difficult for us to tell by x-ray films. Only in the presence of coarse nodularity of the pleura would we suspect a malignant process.

DR. KING: Absence of a nodular pleura does not rule it out?

DR. MCCORT: No.

DR. KING: Is this consistent with "thickened pleura"?

DR. MCCORT: There may be a small amount of fluid, as well.

DR. KING: I shall make the diagnosis of bronchogenic carcinoma with a possible superimposed tuberculosis. One has also to consider what is occurring a good many times these days: an unusual mycotic infection of some sort. I shall put down tuberculosis and mycotic infection as possibilities.

A PHYSICIAN: I should like to ask Dr. King what type of hemoptysis this patient had. Is it not consistent with the type that Dr. Edward D. Churchill describes with carcinoma?

DR. KING: No; this is not that type. Dr. Churchill has frequency spoken of the characteristic hemoptysis of bronchogenic carcinoma, occurring daily and in small amounts for a long period of time.

DR. MCCORT: I might say that in the Radiology Department we followed the same reasoning and arrived at the same conclusion. Enlargement of the interlobar lymph nodes on the left side and the lymph nodes at the bifurcation could be explained by the presence of metastases secondary to a carcinoma in the left lower lobe. We could not satisfactorily explain enlargement of the right interlobar lymph nodes on this basis.

DR. BENEDICT: In addition to the findings described, the patient had a wide and rather fixed carina, and I thought from that it was inoperable carcinoma.

DR. KING: Does tuberculosis give this picture from a bronchoscopic standpoint?

DR. BENEDICT: No; I have never seen it.

DR. KING: Or mycotic infections?

DR. BENEDICT: I have not bronchoscoped enough patients with mycotic infections to know, but I do not believe so.

DR. CASTLEMAN: Dr. Soutter, would you tell us the opinion on the ward, and why you operated after Dr. Benedict said it was inoperable?

DR. LAMAR SOUTTER: That is worthy of some explanation. We felt, as did Dr. King, that this patient had a carcinoma of the lung that had metastasized to the mediastinal lymph nodes, and that it was incurable by operation. It has been our experience that it is generally unwise to attempt the removal of tumors that have spread beyond the confines of the lung. The mortality is high, and the survival is no longer than if the disease had been treated by radiation therapy. But there are three groups of patients on whom a so-called palliative operation should be undertaken. They are those who have a severe degree of infection distal to a blocked bronchus, those who have severe repeated hemoptyses and those who have pain in the chest wall due to direct extension of tumor that cannot be readily controlled by other means. We felt that this patient fell into the group of those who have a severe infection distal to a bronchus blocked by tumor. He had a very good response to antibiotics. However, we decided — because of the bleeding and the fact that the infection could not be controlled by antibiotics, and in spite of the very bad prognosis given by bronchoscopy — that we should try to remove the infected portion of the lung. We felt it unwise to give him x-ray therapy in the presence of an abscess. When we opened the chest cavity, there were adhesions around the lower lobe of the lung. The diaphragm was tented, with dense adhesions between it and the lower lobe, and it was difficult to free up by sharp dissection. When we freed up the lung and palpated the mediastinum, we found, to our surprise, that the lymph nodes were small; and they did not have the grayish appearance of metastatic carcinoma. The bronchus was thickened well above the upper-lobe bronchus. It was impossible to tell if this thickening was due to carcinoma. As there was apparently normal bronchus proximal to the thickened area, and as a bronchotomy for the purpose of viewing a tumor would have meant contamination of the chest cavity with tumor cells, I felt it wiser to perform a pneumonectomy as a better cancer operation. The pneumonectomy was carried out without difficulty.

CLINICAL DIAGNOSIS

Bronchogenic carcinoma.

DR. KING'S DIAGNOSES

Bronchogenic carcinoma with metastases to the pleura and mediastinum.
?Tuberculosis.
?Mycotic infection.

ANATOMICAL DIAGNOSIS

Pneumonitis, severe, organized, with cavity formation.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The left lung showed a normal upper lobe, and a lower lobe that was markedly collapsed, with a very thick pleura around it. There were several cavities, with marked pneumonitis surrounding them. The bronchus was thickened, but in no place were we able to find any tumor. Sections — and we have many all through

the bronchus in all areas of the lobe — showed very severe pneumonitis with organization of exudate within the alveoli. I believe this began as pneumonia, with organization of the pneumonic process and secondary abscess cavities. We were unable to culture any particular organism. There was no evidence of a mycotic infection — and we looked very carefully for them.

DR. FRANCIS M. RACKEMANN: I should like to ask Dr. Benedict if he would tell us about the satisfactory biopsy. If it was satisfactory, why did it not show anything?

DR. BENEDICT: We took a piece of tissue that I thought was adequate. When I found the report was negative for cancer, I wanted to repeat the bronchoscopy.

DR. SOUTTER: We had two bronchoscopies, which we felt were enough. Sometimes it is impossible to reach the actual tumor itself with the bronchoscopic biopsy forceps, although it seems well visualized. If we had known the correct diagnosis we should not have proceeded with surgery but should have given him a longer course of medical therapy. It is fortunate that he made a very good recovery and went home at the end of twelve days.

DR. CASTLEMAN: I do not believe that even under medical therapy the lung would function again. The question is whether you would remove the lower lobe at some later date.

DR. SOUTTER: That is true. However, we should have preferred to try him on medical therapy before attempting surgery.

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2. Smith, F. R., and Boyden, E. A. Analysis of variations of segmental bronchi of right lower lobe of 50 injected lungs. *J. Thoracic Surg.* 18:195-215, 1949.
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CASE 37042

PRESENTATION OF CASE

A fifty-two-year-old man entered the hospital because of abdominal pain.

Three months before entry, the patient became aware of the gradual onset of periumbilical pain, confined at first to an area 3 to 5 cm. in diameter. The pain usually came on at night, did not radiate and was not made worse by palpation, ingestion of food or changing position. It occurred at two- to seven-day intervals and usually lasted for two or three hours. At first the pain was tolerated relatively well, and the only other symptom was some increase in flatulence. However, in the course of a few weeks the pain increased in severity, frequency and duration. For the first time he noted that it radiated straight through to the back at the level of the tenth to the twelfth thoracic vertebra and was felt well out to both sides of the spine. During a two-week cruise at this time, he became completely asymptomatic. However, one month before entry the pain recurred more severely, spread to include most of the lower abdomen and seemed to be aggravated by ingestion of food. He compared the pain to "being hit in the pit of the stomach by a baseball." The symptoms gradually limited his physical activity and began to interfere with his sleep. He had no change in bowel habits, and although he noted no clay-colored, bloody or tarry stools, he had noticed occasional light tan stools. He became aware of some increase in "rumbling and flatulence," gradually increasing anorexia and a ten-pound weight loss during the three months prior to entry. He had only two episodes of vomiting. There were no symptoms relative to the urinary tract. During the course of the illness he visited two different physicians and had a gall bladder series, a gastrointestinal series and an intravenous pyelogram, all of which were normal except for the finding of some small calcified areas thought to be pancreatic calculi.

The only significant item in the past history was an episode of jaundice that lasted for two months, and about which he remembered no details but thought the diagnosis was "flu." He had never had clay-colored stools, dark urine or abdominal pain. He had had an appendectomy twelve or fifteen years ago, without residual symptoms other than some flatulence.

Physical examination revealed deep tenderness in the right midabdomen. The liver edge was palpated and described as being sharp by one examiner. The lungs were clear, and examination of the heart was not remarkable. He had an old healed appendectomy scar and hemorrhoids.

The temperature, pulse and respirations were normal. The blood pressure was 95 systolic, 70 diastolic.

The urine was normal. Examination of the blood disclosed a hemoglobin of 14.4 gm., and a white-cell count of 6900, with 58 per cent neutrophils. The serum amylase was 43 units per 100 cc. The stool was guaiac negative on two examinations. The sedimentation rate was 0.6 mm. per minute, and the hematocrit was 44 per cent. Drainage of the duodenum after twelve hours' fasting returned copious amounts of yellow creamy material. After 1 mg. of prostigmine was given intramuscularly, there was no change in drainage. The sediment showed many red blood cells, a few neutrophils and moderate numbers of sheets and clumps of epithelial cells of goblet type, all of which were bile stained. No calcium, bilirubin crystals or cholesterol plates were present. Thirty minutes after 40 cc. of 50 per cent magnesium sulfate was given through the tube, the return was clear blackish bile with small blood clots. Examination of this sediment showed many more red blood cells and epithelial cells,

occasional neutrophils and no calcium, bilirubin or cholesterol. Cytological examination of a smear was negative. X-ray examination of the abdomen showed a cluster of calculi, the largest of which measured more than 1 cm. in diameter, situated in the right upper abdomen posteriorly apparently within the head of the pancreas (Fig. 1 and 2). Examination of the gastrointestinal tract revealed a normal-appearing esophagus. The gastric folds were somewhat prominent. The duodenal bulb appeared normal. The mucosal folds within the second portion of the duodenum were wide, and there was a small defect at the midportion of the inner aspect of the duodenum that was thought to represent the swollen ampulla. After a glass of ice water the transit time through the small bowel was normal.

On the ninth hospital day an operation was performed.

Differential Diagnosis

Dr. Marshall K. Bartlett*: May we see the x-ray films, Dr. Hanelin?

Dr. Joseph Hanelin: Films of the abdomen show the calcification described within the abdomen,

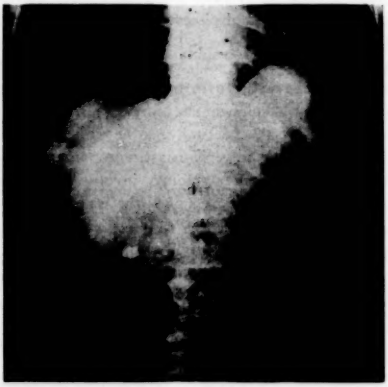

Figure 1.

in the right upper quadrant, and rather typically in the position of the pancreas, further corroborated by a gastrointestinal examination, which shows the calcium densities to lie within the loop of the duodenum. The esophagus, stomach and duodenum are not unusual, except for widening of the duodenal folds in the second portion and a small defect thought to represent a swollen ampulla. Films of the small bowel show no definite organic abnormality or any evidence of functional disorder. There is no widening of the duodenal loop that I can see.

Dr. Bartlett: This, then, was a three-month story of increasing abdominal pain, which was at first periumbilical and did not radiate. Gradually the pain became more severe, radiated to the back and laterally to both sides of the spine, and finally included most of the lower abdomen. I assume that

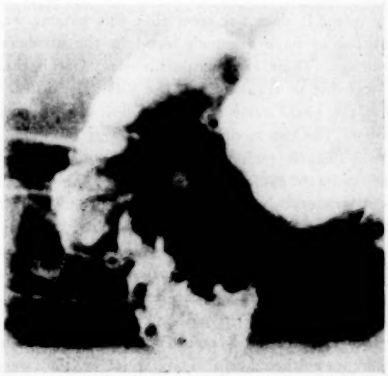

Figure 2.

the first physician who heard this history had a good many things in mind when he began his investigation. Obviously the cause could be gall bladder disease, or something less common. A good many of the possibilities have been more or less ruled out for me. I shall take advantage of the studies, and limit the discussion to what are perhaps the two most likely possibilities.

I think it is fair to rule out the gall bladder and perhaps the biliary tree by means of the negative x-ray examinations done before the patient was admitted; likewise, I shall exclude the stomach and the small bowel and settle down to a discussion of what lesion in the pancreas or duodenum may have been present to account for this chain of events. It is a perfectly good background for pancreatic calculi; and they are present in the x-ray films. That certainly could account for the pain, for the various other intestinal disturbances and for the weight loss — as far as I can see, for the entire clinical picture. However, some of the laboratory data, and the x-ray appearance of a filling defect in the region of the ampulla, bring up the question whether there may have been something else. Specifically, I began to wonder if there was a neo-

*Assistant visiting surgeon, Massachusetts General Hospital.

plasm in the duodenum. There was something in the region of the ampulla that appeared bigger than it should be. The duodenal drainage was interesting — and, to me, rather unusual in some of the findings. I ventured to inquire of some of my medical brethren about this duodenal drainage and found them very uncommunicative, which I interpreted as meaning that they knew more about this case than I was supposed to. So, without benefit of any help from them, I shall have to go along on my own. It does not seem that this patient was entitled to have so much blood in the duodenal drainage. There are two possibilities. One is that it was due to trauma from the tube; the other is that the blood came from some lesion, such as a tumor. The two stool guaiac tests were both negative. That is perhaps a little encouragement, if one wants to explain the red cells on the basis of local trauma during the examination. "Sheets and clumps of epithelial cells of goblet type" is interesting, but it does not tell me very much. There are several possible sources for these cells, and I do not see how I can determine their exact source.

DR. DANIEL S. ELLIS: They were just high, columnar epithelial cells. I would not say they were goblet cells.

DR. BARTLETT: Which makes them even less specific.

The absence of bilirubin and cholesterol plates again does not help me to distinguish between a neoplasm of the duodenum and simply pancreatic lithiasis. I do not see how I can settle this definitely. I suspect that the surgeon who embarked on the operation was not clear in his own mind whether or not he would find a process in the duodenum in addition to what was going on in the pancreas. I am going to put my money on saying that this process was due to one disease only — pancreatic lithiasis; that the entire picture was due to that, and that the findings that did not seem to fit were purely incidental.

The surgeon, on arriving inside the abdominal cavity, still had a problem. He had to determine from a local examination whether or not there was something in the duodenum, because on that he would have to base his choice of operative procedure. If he could establish a diagnosis of a neoplasm of the duodenum, or ampulla or head of the pancreas, which could behave in the same way, obviously the only aggressive approach would be a radical removal, unless it was inoperable. It seems to me that the long story and the severe pain are against such a lesion. A neoplasm of the ampulla or of the head of the pancreas frequently causes pain and loss of weight, but the pain is not so severe, as a rule, as in this case. I would expect such a lesion to produce jaundice. I think the surgeon will conclude, at the end of the local examination, that there was no neoplasm and will be faced with the decision of what to do to relieve the symptoms of pancreatic calculi.

DR. BENJAMIN CASTLEMAN: What would you do then?

DR. BARTLETT: There are various approaches to the problem, and I am sure the last chapter has not yet been written. In general, there are three types of approach. One is to remove the gall bladder, explore the common duct and divide the sphincter of the ampulla. A special instrument has been devised for this purpose, with a cutting blade on its end, that is passed down through the duct. A number of cases have been reported, including some cases of pancreatic lithiasis, in which this procedure has been followed with good results. A second approach — an indirect one — is to attempt to relieve the pain by dividing the afferent pathways by a splanchnicectomy. This frequently must be bilateral, eventually, to be effective. This approach has various enthusiastic proponents. The third, a total pancreatectomy, involves the most radical surgery, but removes the source of the difficulty. I would not like to guess which of these approaches the surgeon chose in this case.

DR. CHESTER M. JONES: Dr. Arthur Allen, Dr. Ellis and I were in agreement that pancreatic lithiasis was the primary diagnosis. However, I was not sure in my own mind whether this calculus was in the pancreatic duct or whether it was possibly in a dilated ampulla where the pancreatic duct and common duct came together. The absence of jaundice did not rule out the possibility that it could have been in the common duct. It was not a gallstone, as far as we could tell; the gall bladder function was normal. Almost always, if biliary calculi are present, the duodenal drainage will show calcium bilirubin crystals or cholesterol, or both, and this showed no crystalline elements whatever. The presence of blood was very up-

setting. It was not caused by trauma or excessive suction. Is that not right, Dr. Ellis?

Dr. Ellis: There was no suction used at all. There was a copious flow of material through the tube the whole time the drainage was taking place.

Dr. Jones: Because of the blood, we were prepared for, although we did not anticipate, a cancer as well as the pancreatic calculus here. Just before the operation, Dr. Allen and I talked it over and decided that if there was no obvious malignant process, probably the move to make would be a partial resection of the head of the pancreas, with implantation of the ducts and gastrojejunostomy rather than a total pancreatectomy, which would have left him with a continuing problem of no minor degree. That is a real problem to live with. We hoped to do that kind of surgery, but the decision had to be made on the table. There was tenderness over the area of the calculus, which also made us feel that there was a good deal of inflammatory disease around the area.

One thing I should like to ask Dr. Hanelin is: Is the irregularity in the inner curve of the duodenum due to inflammation in the head of the pancreas? We have seen that arising from adjacent lymph nodes in hepatitis.

Dr. Hanelin: I think, in this particular instance, probably the enlargement of the nodes in the common duct may have been responsible for a great deal of the irregularity.

Dr. John B. Stanbury: Do you ever see abscess formation behind a pancreatic stone?

Dr. Jones: I think so.

Dr. Bartlett: There may be cyst formation, and I see no reason why this should not become an abscess.

Dr. Ellis: We thought something like that was going on in this case. There is an area of translucency around the stone in all the x-ray pictures. Dr. Laurence L. Robbins thought there might be some necrotic tissue around it, with abscess formation.

Clinical Diagnosis

Pancreatic lithiasis.

Dr. Bartlett's Diagnosis

Pancreatic lithiasis.

Anatomical Diagnoses

Pancreatic lithiasis, with obstruction of pancreatic duct, chronic.

Fibrosis and chronic inflammation of pancreas.

Pathological Discussion

Dr. Castleman: Perhaps one of the surgeons could tell us what was done at operation.

Dr. Grant V. Rodkey: Dr. Bartlett has accurately predicted the problem that Dr. Allen faced when he entered the abdomen. The initial exploration did not reveal any evidence of a neoplasm in the duodenum or ampulla. However, the head of the pancreas was considerably enlarged and was definitely indurated. There were areas that seemed to represent stones in the head of the pancreas, but it was difficult to define any individual stone. In particular, we were not able to identify the large stone that was suspected of obstructing the main pancreatic duct. It was not possible to be sure what we were dealing with, even at that point in the operation. Therefore Dr. Allen did a resection of the main portion of the pancreas, removing about two thirds of it. The distal stomach and the entire duodenum were resected en bloc with the specimen. As far as we could tell, that seemed to remove all the grossly diseased tissue. The tail of the pancreas did not seem to be involved — it was not edematous or swollen, and it contained no palpable stones. The pancreatic duct was distended to about 1 cm. in diameter, and was full of clear serous fluid.

Dr. Castleman: I was called to the operating room and was presented with the specimen, which I dissected with a good deal of difficulty. I could feel the big stone, but I could not get it out. Finally, after opening the duodenum and finding the papilla, I opened the common bile duct, which was slightly thickened but free from stones. Through the opened bile duct 7 mm. from the papilla I was able to feel the stone, which was impacted in the markedly dilated pancreatic duct (Fig. 3). Other calculi were scattered throughout the pancreatic parenchyma, or what was left of it, because in the microscopic sections we could find no acinar tissue, and only an occasional islet cell. The parenchyma had been destroyed and replaced by fibrous tissue, in which

were markedly distended pancreatic ducts. It is interesting that this patient had no jaundice, even though the stone was contiguous to the wall of the common bile duct.

Would you explain the various anastomoses, Dr. Rodkey?

DR. RODKEY: The anastomoses performed are rather interesting. We anastomosed the common hepatic duct to the end of the jejunum, which had

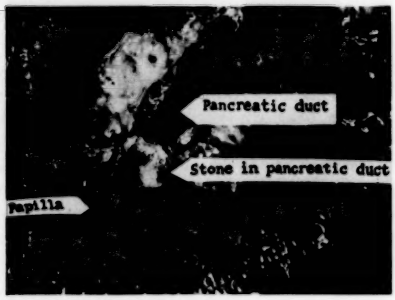

FIGURE 3.

been brought up in such a way as to enfold its resected margin. The anastomosis was performed over a short segment of soft rubber catheter, which was anchored to the common hepatic duct by a catheter suture. The pancreatic duct also was cannulated with a catheter, and the cut end of the pancreas was implanted into the side of the jejunum at a point about 4 cm. distal to the previous anastomosis. The stomach was then anastomosed to the antimesenteric border of the jejunum, approximately 4 cm. distal to the pancreatic jejunostomy.

Dr. Allen would like to have it said that he considered another possible approach in this patient — a splanchnicectomy, to ablate the pain pathways. However, he felt that the problem of obstruction to the pancreatic duct would not be solved by that procedure and that the result would be unsatisfactory. He did have a patient four years ago who had small pancreatic stones who was effectively relieved of pain by bilateral splanchnicectomy.

DR. BARTLETT: Do you know anything about the formation of stones within the duct of the pancreas, as contrasted with stone formation in pancreatic tissue?

DR. CASTLEMAN: It is rare to find stones within the duct; in most cases the stones are in the parenchyma. I would guess that there were two possibilities here — either a stone perforated into the duct and grew, or stasis of secretions within the duct produced it.

DR. JONES: I have the same impression that you have. One fact that was of some importance here was the anatomic arrangement of the pancreatic duct and its entrance into the common duct. In this case it was not too difficult to get stasis in the pancreatic duct. The case that Dr. Rodkey referred to, in which a splanchnicectomy was done, was one of calcification of the pancreas; as far as we could tell it was not associated with free calculi in the duct. I think relief by splanchnicectomy is much greater in pain from calcification of the pancreas than with a calculus in the duct that is causing colic.

NEW HAMPSHIRE MEDICAL SOCIETY

PROCEEDINGS OF THE ONE HUNDRED AND FIFTY-NINTH ANNIVERSARY (Concluded)

House of Delegates, September 12, 1950

THE second meeting of the House of Delegates convened at the Mount Washington Hotel, Bretton Woods, New Hampshire, on Tuesday, September 12, 1950, at 8:30 a.m., with Dr. B. Read Lewin, of Claremont, as the Speaker.

The following delegates answered the roll call:

The President, *ex-officio*
The Vice-President, *ex-officio*
The Secretary-Treasurer, *ex-officio*
W. J. Paul Dye, Wolfeboro
Ralph W. Tuttle, Laconia (alternate for Francis J. C. Dube)
Louvane A. Fox, Keene
Marjorie Parsons, Colebrook
Everett C. Campbell, Woodsville
Reginald K. House, Hanover
Leslie K. Sycamore, Hanover
Harris E. Powers, Manchester
Richard T. Mulvanity, Nashua
Raymond H. Marcotte, Nashua
Frank F. Flagg, Nashua
Edward D. Hagerty, Manchester
Lloyd L. Wells, Manchester (alternate for Oscar Burns)
Warren H. Butterfield, Concord
Edward V. Putnam, Warner
Francis Brown, Henniker
Frederick S. Gray, Portsmouth
Louis C. Theobald, Exeter
Henry Saltonstall, Exeter
Albert E. Barcomb, Rochester
Edna Walck, Dover
Francis H. Nolin, Claremont (alternate for Addison Roe)

The speaker declared a quorum present. The president appointed William Gifford, of Colebrook, as alternate for Julius Israel, Thomas G. Cogswell, of Concord, as alternate for William D. Penhale, and Francis H. Nolin, of Claremont, as alternate for Addison Roe.

Dr. Dye moved that the By-laws be suspended so that changes in the *Constitution and By-laws* could be taken before the report of the Committee on Nominations was made.

This motion was duly seconded and was carried.

Dr. Dye then moved that the following changes in the Constitution be read before the General Assembly and subsequently, according to the provisions concerning amendments, that these changes be transmitted to the various county secretaries two months, or sooner, before the next annual meeting:

Article V, change to read: "and (2), ex-officiis, the immediate Past President, the President, the President-Elect, the Vice-President, and the Secretary and Treasurer."

In Article VII, strike out Section 2.

Article VIII, Section 1, change to read: "The Officers of this Society shall be a President, a President-Elect, a Vice-President, a Speaker and a Vice-Speaker of the House of Delegates, a Secretary and Treasurer, ten Councilors (one from each County), and a Board of three Trustees."

Article VIII, Section 2. Change first line to read: "The President-Elect shall be elected for a term of one year, succeeding thereafter to the office of President for a term of one year. Succession shall also take place upon the removal, death, resignation or retirement of the President. The Vice-President shall be elected for a term of one year."

In the second sentence of the present Section 2 of Article VIII, change "Secretary-Treasurer" to "Secretary and Treasurer."

The motion was then duly seconded and was carried.

Dr. Dye then proposed the following changes in the By-laws:

Chapter I, Section 6, change the whole section to read as follows:

"Any physician who has been a member of this Society for a term of fifteen years, and is either not less than sixty-five years of age, or partially or totally disabled, and to whom the payment of dues would be a financial hardship, on the request of his County Society, may be made a Life Member by a majority vote of the House of Delegates. Life Members shall have the same rights and privileges as other members, but shall not be required to pay dues."

Chapter II, Section 1. Add the following: " . . . or as determined by the Executive Committee."

Chapter IV, Section 1. Change to read: "The first meeting of the House of Delegates shall be held whenever designated by the President or the Executive Committee" and so forth.

Chapter V, Section 2. Strike out "at the first meeting of the annual session." For this, substitute "at his discretion." Strike out "President and." Strike out "President or."

Chapter VI, Section 1. Change the first line to read: "The President shall preside at all meetings of the Society or Executive Committee" and so forth.

Chapter VIII, Section 1. The standing committees shall be as follows:

1. An executive committee.
2. A committee on arrangements.
3. A committee on scientific work.
4. A committee on medical economics.
5. An advisory committee on jurisprudence.
6. A committee on tuberculosis.
7. A committee on mental hygiene.
8. A committee on the control of cancer.
9. A committee on medical education and hospitals.
10. A committee on maternal health and infant welfare.
11. A committee to the Council of the New England State Medical Societies.
12. A committee on industrial health.
13. A committee on rural medical service, and such other committees as may be necessary. Such committees shall be elected by the House of Delegates unless otherwise provided."

In the above, "A Committee on Public Relations" has been stricken out, and "An Executive Committee" substituted therefor. "A Committee on Publications" has also been stricken out.

The numerical sequence of committees has been changed to conform with deletions and substitutions, and the descriptive sections of Chapter VIII will, accordingly, conform to the above sequence.

Section 2, change to read as follows: "The Executive Committee shall consist of the immediate Past President, President, Vice-President, Secretary-Treasurer, Speaker of the House of Delegates, and Vice-Speaker" and so forth down through "annual session" after which add, "or at other designated times." Also add, "The President shall be Chairman of this Committee. The Committee shall administer and advise concerning the affairs and policies of the Society and may designate the time and place for special and regular meetings of the House of Delegates and of the Society. It may employ such secretarial staff as is necessary for the proper conduct of the Society's affairs. It shall keep records of its transactions to be available to the House of Delegates. It shall prepare the budget for the ensuing calendar year for submission to the House of Delegates."

Chapter XI, Section 4. In the second line, change "accurate" to "a," and strike out "all of which shall be at all times accessible to every member of the New Hampshire Medical Society." Strike out "also of the accumulated evidence" and so forth to the end of the paragraph.

Chapter X, Section 2. Strike out "approved by the House of Delegates on a call of the ayes and noes." Substitute therefor "by a majority vote of the House of Delegates."

Dr. Brown moved the adoption of these changes in our By-laws.

This motion was duly seconded and was carried.

Secretary Smith then moved that the House rise from executive session and resume the regular order of business.

This motion was duly seconded and was carried.

Dr. Frederick S. Gray, for the Committee on Nominations, presented the following nominations:

PRESIDENT

Harris E. Powers, of Hillsborough County
James A. Ferguson, of Coos County
Walter H. Lacey, of Cheshire County

VICE-PRESIDENT

The two men who are not elected as president and W. J. Paul Dye, of Carroll County

SECRETARY-TREASURER

Deering G. Smith, of Hillsborough County (it was also recommended that the Executive Committee appoint an assistant secretary)

COUNCILOR FOR HILLSBOROUGH COUNTY

Timothy F. Rock, of Nashua

COUNCILOR FOR MERRIMACK COUNTY

Charles H. Parsons, of Concord

TRUSTEE FOR TWO YEARS

Ralph W. Tuttle, of Carroll County

TRUSTEE FOR THREE YEARS

James W. Jameson, of Merrimack County

SPEAKER OF THE HOUSE OF DELEGATES

B. Read Lewin, of Sullivan County

VICE-SPEAKER OF THE HOUSE OF DELEGATES

Albert Barcomb, of Strafford County

NECROLOGIST

Ralph W. Tuttle, of Carroll County

Dr. Harris E. Powers was elected president, Dr. W. J. Paul Dye as vice-president and Dr. Deering G. Smith as secretary-treasurer. Dr. Timothy F. Rock was elected councilor for Hillsborough County, Dr. Charles H. Parsons councilor for Merrimack County, Dr. Ralph W. Tuttle trustee for two years, Dr. James W. Jameson trustee for three years, Dr. B. Read Lewin speaker of the House of Delegates for the ensuing year, Dr. Albert Barcomb vice-speaker of the House of Delegates and Dr. Ralph W. Tuttle necrologist.

The following members were elected to the standing committees indicated:

Amendments to Constitution and By-laws: W. J. Paul Dye, Carroll County; Henry Saltonstall, Rockingham County; John H. Branson, Merrimack County.

Child Health: Thomas B. Walker, Portsmouth; Ursula G. Sanders, Concord; Marion Fairfield, Nashua.

Control of Cancer: George C. Wilkins, Manchester; Ralph E. Miller, Hanover; George F. Dwinell, Manchester; Walter H. Lacey, Keene; John R. Perley, Laconia; James W. Jameson, Concord.

Council of New England Medical Societies: John P. Bowler, Hanover; Ralph W. Tuttle, Wolfeboro; Carleton R. Metcalf, Concord.

Industrial Health: David W. Parker, Manchester; Francis H. Nolin, Claremont; Charles F. Keeley, Claremont; Robert W. Holmes, Keene; Robert Kaschub, Berlin; Daniel F. McCooey, Dover; John C. Eckels, Laconia; Robert Flanders, Manchester; John H. Kennard, Manchester; Timothy F. Rock, Nashua; Charles I. Umpa, Nashua.

Maternity and Infancy: Robert O. Blood, Concord; Robert N. Lord, Manchester; Frederick S. Gray, Portsmouth.

Medical Economics: Leslie K. Sycamore, Hanover; Norman W. Crisp, Nashua; Joseph N. Friborg, Manchester.

Medical Education and Hospitals: John P. Bowler, Hanover; Harold I. Loverud, Manchester; Howard P. Sawyer, Brookfield.

Mental Hygiene: Arthur B. Howard, Concord; Edward S. Morris, Laconia; Simon Stone, Manchester.

National Emergency Medical Service: Daniel J. Sullivan, Nashua; Joseph M. McCarthy, Concord; Clarence E. Dunbar, Manchester; Bernard J. Manning, Dover; John C. Eckels, Laconia; John B. Holyoke, Hanover.

Public Health: S. G. Griffin, Portsmouth; Robert C. Storrs, Hanover; Thomas Dudley, Concord.

Rural Health: William F. Putnam, Lyme; William P. Clough, Jr., New London; Samuel Feiner, Ashland.

Tuberculosis: Robert Kerr, Manchester; Frank G. Seldon, Manchester; John D. Spring, Nashua.

Scientific Work: Deering G. Smith, Nashua; Rolf Lium, Portsmouth; M. Dawson Tyson, Hanover.

Dr. Brown moved the adoption of the following resolutions:

WHEREAS, one of the purposes of the New Hampshire Medical Society is the enlightenment and direction of public opinion in medical matters, and

WHEREAS, one step in the field of applied public relations is a closer co-operation with the press and radio,

NOW, THEREFORE, BE IT RESOLVED: That

1. The officers of the New Hampshire Medical Society shall be available at all times to the representatives of the press and radio, in order that authentic information may be obtained as promptly as possible on health and medical subjects. If the information is not immediately available, it shall be the function of the executive office, or such individual or representative of the Society as the Executive Committee may direct, to obtain the information desired or locate a competent authority from whom the press or radio may obtain it directly; and that

2. Officers, committee chairmen or designated spokesmen of the New Hampshire Medical Society may be quoted by name in matters of public interest for the purpose of authenticating information given. This shall not be considered by their colleagues a breach of traditional practice of physicians to avoid personal publicity, since it is done in the best interests of the public and the profession. County medical societies are urged to adopt a similar policy with respect to their officers, committee chairmen, and designated spokesmen; and that

3. The New Hampshire Medical Society use its influence to encourage each hospital to have someone available at all times to deal with representatives of the press and radio and that the name of this hospital representative, or his delegated authority in his absence, be available to information and/or switchboard operators, so that inquiries from newspapers may be expedited. Persons delegated to talk with the press and radio should be familiar with the fundamental principles of the code governing relations between the hospitals and the press and radio and within the limits of such code co-operate with the newspapers and radio; and that

4. The Society approves the following fundamental rules to be used by hospitals and newspapers as a minimum standard guide in specific instances:

(a) Hospitals should give the name of the attending physician to the newspaper, when so requested. The newspaper shall not use the physician's name without his consent.

(b) The presence of certain patients in a hospital in whom the public has a rightful interest is news. Their presence should generally be acknowledged by the hospital, unless expressly forbidden by the patient or attending physician.

(c) In emergency cases, the following items of public interest, which are a matter of police or fire department record, and are available from these records, shall be given promptly by the hospitals:

Name, age, sex, marital status, address, occupation and employer.

Nature of the accident — such as automobile, explosion, shooting, etc.

Extent of injuries — such as fractures, burns, wounds and so forth and to what part of the body. It is understood that, pending complete diagnosis, these statements may, of necessity, have to be hedged with "possible fractures," — "condition apparently good, fair or serious," etc.

(d) When newspapers request the privilege of photographing a patient in the hospital, such permission will only be given (A), if the patient gives consent, and if, in the opinion of the doctor in charge of the case, the patient's condition will not be jeopardized, and (B) if the patient is a minor, the parents or guardian are willing to have a photograph taken.

(e) The death of any patient is presumed to be a matter of public record. A statement that the patient has died should be made by the hospital.

(f) Births are a matter of public record and hospitals should assume the obligation to give full information concerning the same, including facts which appear in public records, such as parents' names, mother's maiden name, parents' address and time of birth, provided the mother consents to publication of the birth.

The motion was duly seconded and was carried.

Speaker Lewin: Next is the supplemental report of the Committee on Emergency Medical Service by Dr. Sullivan.

Dr. Brown moved that the House of Delegates authorize and direct the president of the Society to request all hospitals in the State to carry out the recommendations numbered 1 to 6 inclusive, in the Supplementary Report of the Committee on Emergency Medical Service, to request the Commissioner of Education to use his influence to have recommendation No. 4 of the Supplementary Report of the Committee put into effect in the schools of nursing under his jurisdiction ("That all hospitals having training schools for nurses teach student nurses to withdraw venous blood and to administer intravenous fluids and medications and transfusions") and to request the Commissioner of Education to establish courses in first aid in all the high schools in the State.

These motions were duly seconded and were carried.

Dr. Parsons moved that the matter of co-ordinating medical and selective service be taken from the table. The motion was duly seconded and was carried.

Dr. Hagerty moved that if a committee were formed it be headed by a World War II veteran for correlation of military aid, in the form of doctors from the State, and that the Committee on Emergency Medical Service be empowered to be responsible to carry on the duties of procurement and assignment. The motion was seconded and carried.

The following names were proposed for life membership:

Carroll County: Harlan F. Curtis, of Wolfeboro.

Cheshire County: J. Dellinger Barney, of Boston, Massachusetts, and Harry G. Williams, of Keene.

Coos County: Guy W. Barbour, of Stewartstown, and Henry L. Dyer, of Berlin.

Grafton County: Sarah C. Johnson, of Franconia, and Elmer M. Miller, of Woodsville.

Hillsborough County: George B. Hoitt, Leopold T. Togus, and Howard A. Streeter, all of Manchester.

Merrimack County: Henry H. Amsden, Clarence E. Butterfield, Fred S. Eveleth, Carleton R. Metcalf and Walter C. Rowe, of Concord, William P. Clough, of New London, and Arthur W. White, of Bristol.

Strafford County: Harry O. Chesley, Edward C. Batchelder and John L. Sweeney, of Dover, Joseph L. McLaughlin, of Farmington, Jeremiah J. Morin and Walter J. Roberts, of Rochester, and Thomas J. Morrison, of Somersworth.

State: Arthur P. George, of Haverhill, Massachusetts, and George H. Gray, of Hyannis, Massachusetts.

The life membership of these members was approved.

Dr. Dye then moved that the life membership be made retroactive to the date on which the members were elected as such in their various county societies.

The motion was duly seconded and was carried.

Dr. Mulvanity then proposed the following resolution:

Resolved: That it is the opinion of this House of Delegates that no physician who falls in categories 1, 2 and 3 in the law regarding Selective Service for physicians should be deferred because of civilian needs, until the effort has been made, and has failed, to replace him in civilian capacity by a physician in category 4.

Dr. Saltonstall moved the adoption of this resolution.

This motion was duly seconded and was carried.

Dr. Gifford read the following letter from the Department of Public Welfare:

In accordance with an established plan of rotation, Dr. Thomas Reid of Dover is retiring as a member of the Medical Advisory Committee on Eye Conditions, which assists the Department of Public Welfare in adequately handling medical matters in connection with the State's blind aid and prevention of blindness program.

To replace Dr. Reid, the department recommended Dr. Hunter, who has accepted our invitation to serve. In order

that the records may be kept up to date, and the State Medical Society may be kept informed on all departmental matters relating to the medical care field, I am writing to request that the House of Delegates approve Dr. Hunter's acceptance to this Committee.

Dr. Gifford moved that the recommendation contained in the letter be approved.

This motion was duly seconded and was carried.

Dr. Sycamore then moved approval of the following New Hampshire members of the Board of Directors of the New Hampshire–Vermont Physicians' Committee of the Blue Shield: Dr. Leslie K. Sycamore, of Hanover, Charles R. Eastman, of Kingston, Ray W. Pert, of Concord, Frank J. Sulloway, of Concord, Right Reverend Monsignor J. S. Buckley, of Concord, O. E. Cain, of Keene, Right Reverend John T. Dallas, of Lee, Dr. Francis J. C. Dube, of Center Ossipee, George Fecteau, of Manchester, Dr. Fred Fernald, of Nottingham, Dr. John A. Hunter, of Dover, James M. Langley, of Concord, Dr. Carleton R. Metcalf, of Concord, Dr. J. J. Morin, of Rochester, Dr. Clinton R. Mullins, of Concord, George M. Putnam, of Contoocook, and Dr. Isadore J. Zimmerman, of Manchester.

This motion was duly seconded and was carried.

Dr. Brown moved that the Secretary write letters to the county secretaries, asking that a member of the Blue Shield Committee be elected by the county societies for a term of one year, and that this be done as soon as practicable and that the present members should serve until the county societies elected their representatives.

This motion was duly seconded and was carried.

Dr. Brown moved that the place and the time of the next meeting be left to the Executive Committee.

This motion was duly seconded and was carried.

Dr. Saltonstall moved that the House of Delegates go on record as being in favor of a combined meeting with the Vermont State Medical Society, and as being in favor of accepting an invitation to meet in Vermont, if so offered.

This motion was duly seconded and was carried.

Dr. Dye moved adjournment.

This motion was duly seconded and was carried.

On motion duly made, seconded and carried the meeting of the House of Delegates was adjourned at 12 noon on September 12, 1950.

SPECIAL MEETING OF THE HOUSE OF DELEGATES

A SPECIAL session of the House of Delegates of the New Hampshire Medical Society, called by President Harris E. Powers, was held at the Eagle Hotel, Concord, on October 12, 1950.

In the absence of the Speaker and the Vice-Speaker, the Secretary called the meeting to order at 11:10 a.m. John P. Bowler was elected Speaker, *pro tempore*.

The following delegates answered the roll call:

Reginald F. DeWitt, Belknap
Francis J. C. Dube, Carroll
Louvane A. Fox, Cheshire
Marjorie A. Parsons, Coos
Reginald K. House, Grafton
Oscar Burns, Hillsborough
Edward D. Hagerty, Hillsborough
Richard T. Mulvanity, Hillsborough
Warren H. Butterfield, Merrimack
William D. Penhale, Merrimack
Edward V. Putnam, Merrimack
Frederick S. Gray, Rockingham
Louis S. Theobald, Rockingham
Henry Saltonstall, Rockingham
Edna Walck, Strafford

President Powers appointed as alternate delegates the following, all of whom were present:

John H. Miller, Belknap
Howard P. Sawyer, Carroll
Arthur E. Laidlaw, Cheshire
John P. Bowler, Grafton
Daniel J. Sullivan, Hillsborough
Lloyd L. Wells, Hillsborough
James W. Jameson, Merrimack
Stanley J. Kuk, Sullivan

The reading of the minutes of the previous meeting was dispensed with.

The President stated that the meeting was called to make recommendations as to the constituency of the state and local subcommittees on physicians provided for by the so-called doctor draft law. He read a telegram sent to Dr. Bowler by Dr. Howard A. Rusk, chairman of the National Advisory Committee on the Selection of Doctors, Dentists and Allied Specialists, requesting him to serve as chairman of the New Hampshire advisory committee. Dr. Bowler acceded to the request.

Dr. Hagerty moved that the members of the Committee on Emergency Medical Service be recommended as members of the volunteer advisory subcommittee of physicians at the state level. These members were as follows: Drs. Daniel J. Sullivan, Nashua, *chairman*; Clarence E. Dunbar, Manchester; John B. Holyoke, Hanover; John C. Eckels, Laconia; Joseph M. McCarthy, Concord; and Bernard J. Manning, Dover.

After considerable discussion about representation of each county on the committee and the method of choice of these representatives, the motion was carried.

It was then voted that each county *not* represented by the above recommendation recommend a member to be chosen by vote of the respective county medical society (these counties were Carroll, Cheshire, Coos, Rockingham and Sullivan).

Finally, it was voted after discussion that a resolution be sent to the president of each county medical society asking that it elect three physicians who would be recommended as members of the local volunteer advisory subcommittee on the selection of physicians.

The meeting adjourned at 12:35 p.m.

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*Representing the New Hampshire Medical Society.

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GREEN LIGHT FOR ACTION

THERE is something fantastic, in this fruitful land where so much has been done and so much is being planned for the amelioration of man's lot, in the idea of making preparations for a series of limited holocausts. It has been accepted, nevertheless, that even these spacious skies can be rent by atomic explosions, these waves of amber grain withered by deadly biological showers and the high walls of these cities made to fall like those of Jericho. It can happen here as it has happened elsewhere, for when the seeds of the tempest have been sown, the whirlwind may be the harvest.

Comfort, however, may be derived, at such a critical period in this young nation's history, from the fact that the resistive quality of its people has at last been aroused to the point where they are again determined to have a hand in the direction of their own destiny, come holocaust, hell or high water.

Many states and communities have already gone the first mile in making their plans for civil defense, subject to the pattern that has been so long awaited from the nation's capital. Like other civil organizations, the Massachusetts Medical Society has for many months had a committee on emergency service ready for a go-ahead signal; and its program for statewide medical mobilization in the event of an emergency, published a week ago in the *Journal*, came from the hands of the co-chairmen of this committee, and was cleared through the office of the chief of the medical and health division of the civil defense organization of the Commonwealth.

Among the community programs designed by patriotic and energetic citizens, to be activated within the framework established in Washington, the one developed in Concord, Massachusetts, is an outstanding example. It will be described in next week's *Journal*.

The 260-page volume comprising the national civil defense program for health services and special weapons defense was finally released on December 27. A model of comprehensiveness, it is now available at the Government Printing Office, for a consideration. Its principles should become familiar to all who are in any way affected, and in particular to persons with civil-defense health-service administrative responsibilities.

It happens that American cities under the threat of bombing have previous examples, of which the London blitz and the destruction of Hiroshima were probably the most instructive, by which to guide their planning. Radiation hazards have now to be guarded against, and biological and increasingly dangerous chemical weapons may be used in the assault, but otherwise the danger is one of degree, and an increase in the size of bombs operates under the law of diminishing returns, a doubled explosive force entailing only a quarter increase in the effective radius of the explosion.

The program for mastering the situation is complicated, but modern life has become so; and that intricate network of facilities that is called a city

cannot continue to function in the wake of major destruction without complicated preparations of some magnitude. The only way, in fact, of meeting the challenge in an uncomplicated manner would be by apathy; the only means by which the hazards of survival could be avoided would be the acceptance of obliteration and oblivion.

This will not happen. America has not yet completed its cycle or fulfilled its destiny. Its course is not yet run. Its life has been too short, its civilization too new, its culture too recent; and its heterogeneous population is too virile for it to succumb to any barbarian attack with weapons that have been taken from its own armament. It is still acquiring stature for its eventual role of world leadership.

GUILTY OR GULLIBLE?

THE campaign to milk the unwary and gullible of millions of dollars through the sale of antihistaminic drugs for the prevention and cure of the common cold is again in full swing. This campaign has been stimulated by one of the most widely read women's magazines, which recently ran a full-page advertisement in many leading newspapers. The advertisement reproduced one of the magazine's popular articles entitled "Do Antihistamines Really Work?" It is obviously a well timed attempt to repeat the performance of the first highly publicized article on this subject, which appeared a year earlier in the *Reader's Digest* under the title "Is This at Last Good-By to the Common Cold?"

The present article, like the earlier one, represents a seemingly honest attempt by a well known science writer to answer the question he poses. He is chiefly impressed by the large number of people who have been given antihistamines for colds in certain industrial plants and have claimed that they were benefited by them. He is totally unimpressed by any possible toxic effects from these agents because his personal inquiries have failed to verify certain newspaper headlines about deaths ascribed to the antihistamines, and also because the number of deaths from industrial and highway accidents have not skyrocketed following the popularization of these drugs. The latter arguments are really irrelevant and can serve only as rhetorical diversions, since the factors entering into these deaths and accidents and into their prevention are far too many and too complex for such simple interpretations. The writer merely mentions and dismisses as unimportant, because of the small number of subjects involved, two carefully controlled studies published in the *Journal of the American Medical Association*. He does not even mention many other studies that give clear evidence that the antihistamines have produced none of the favorable effects on the common cold that have been ascribed to them, and he belittles or ignores the critical comments on antihistamines published in some of the leading medical journals.

Comments have previously been made in the *Journal*[1] on the highly relevant studies on this subject that emanated from Cleveland. These studies by Feller and his co-workers[2] showed quite clearly that the antihistaminic drugs in the usually recommended doses have no effect whatever either on the naturally occurring common cold or on other undifferentiated acute respiratory diseases. They showed further that the drug neither prevented nor altered the character, course or duration of experimentally induced common colds in human volunteers. These studies have been completely ignored by the popular science writer. He does mention the report of Brewster's observations among naval personnel that stimulated all the excitement about the antihistamines as preventives and cures of the common cold. However, he either chose to ignore or was not aware of the recently published studies conducted by the personnel of the United States Naval Medical Research Unit No. 4.[3]

In contrast to the earlier and admittedly uncontrolled observations reported by Brewster, the recent studies made at the Great Lakes Naval Training Station were very strictly controlled, and the results were analyzed in great detail. In the first of these studies, an antihistamine was used in prophylactic doses in 352 male recruits throughout their training period. A group comparable in size and stages of training was treated with placebos, and a third similar group was given no treatment at all. A high incidence of acute respiratory diseases occurred in the population during the course of this study (February–April, 1950), the majority of

which were clinically classifiable as the common cold. An epidemic of influenza also occurred during this time, so that a completely satisfactory clinical separation of all cases of influenza from those of other respiratory diseases was not possible. However, no evidence was found that the antihistamines prevented any of these diseases or effected any important alterations in their symptomatology.

In a second study, two antihistaminic drugs (in dosages within the therapeutic range for each) and a placebo were administered prophylactically to 357 male navy recruits during the period April 10 to April 18, 1950. No new cases of influenza were diagnosed during that period of study. Neither of the antihistaminic drugs demonstrated any ability to prevent the common colds that were epidemic in the population. The use of therapeutic doses before the onset of symptoms did not result in the aborting of colds, and did not produce any important alterations in their symptomatology and duration.

In the third study, WAVES suffering from an acute respiratory disease clinically classified as the common cold were admitted in rotation to groups receiving atropine sulfate, a placebo and an antihistaminic drug. A few cases of influenza were included. No evidence was derived that either atropine or the antihistamine aborted colds or effected any important variation in their duration and symptomatology. It was merely observed that the antihistaminic drug had an atropine-like effect on the nasal mucosa. It was concluded that the appearance of nasal mucosa as a criterion of "cure" in the evaluation of these drugs may prove misleading.

In the fourth study, several antihistaminic drugs were issued to volunteers among families of officers in both prophylactic and therapeutic dosage schedules and compared with the use of placebos. There were too few reports of adequate usage of the drugs in the prophylactic schedule to allow any critical evaluation of this aspect. However, those patients reporting the therapeutic usage had equally beneficial results from placebos and from antihistaminic drugs.

Two additional studies, carried out with great care and under carefully controlled conditions, have been recorded in the *Journal*. One of these,[4] from Oberlin College, showed no evidence that the antihistaminic drug used had any important effect in aborting or ameliorating the colds observed among the students who were studied. In that instance, as in the first of the Navy studies just mentioned, two different control groups were also used, one receiving a placebo and the other receiving no therapy. This study also demonstrated the importance of considering the psychologic effect of taking any medications, whether placebos or others, in evaluating their effects on the common cold.

In this issue of the *Journal* there is another paper by a group from Boston University who made an honest and conscientious attempt to determine the value of antihistamines in the common cold. It represents a very carefully controlled study in which every effort was made to analyze all the symptoms and manifestations of the common cold among an intelligent group of co-operative individuals, all of whom received treatment voluntarily when they thought they were afflicted with colds and then reported what they interpreted as the effect of the treatment they received. The authors went to great lengths to arrange these studies so that they would be as foolproof as possible, and so that personal bias could play no part in the evaluation of the results, either by the subjects or by the investigators. Indeed, it was demonstrated that the subjects could not even guess whether they were receiving one of the antihistamines or the placebo used as a control substance. The data accumulated were subjected to careful scrutiny and minute statistical analysis, and left no doubt whatever of the results. There was absolutely no evidence to indicate that the antihistamines had any effect on the occurrence, duration or severity of any of the symptoms ascribed to the common cold.

It must be concluded that none of the carefully controlled studies carried out by competent and reliable investigators have yielded any evidence to justify the claims of manufacturers and advertisers that the antihistamines either prevent or cure the common colds or in any way alter the character, severity and duration of its symptoms. It can only be considered unfortunate that the well known writer of popular science is dazzled by numbers

but remains unimpressed by the importance of controlled observation in the evaluation of a disease like the common cold. Had he considered the evidence critically, he would have answered his question unequivocally: No! The antihistamines have no value in the common cold!

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SPECIALIZED TRAINING IN CLINICAL CHEMISTRY

The personnel problem of the clinical laboratory has grown steadily more acute, particularly in the demanding area of quantitative chemistry. To help in solving this problem, an experimental program has been undertaken during the last two years in the Department of Biochemistry and Nutrition, Tufts College Medical School, in collaboration with the laboratories of the New England Center Hospital.

The plan is to train biochemists specifically for supervisory positions in the chemical laboratory, where good results, it is believed, may be obtained with technicians of brief training and experience, when they are closely supervised by a trained analyst. A chemist so trained should be able to set up analytical procedures, maintaining constant check on them and recognizing sources of error. He should be able also to maintain modern photometric and manometric instruments and to recognize the reasons for their failure, and to train technicians in analytical procedures.

For this program, a very few college graduates are carefully selected for their interest in a career of this sort. They study for the degree of Master of Science in diagnostic chemistry for a period of one and a half to two years, concentrating on practical analytical problems while carrying out laboratory research in analytical methodology. They also become acquainted with the routine nonchemical procedures of the clinical laboratory.

In view of the growing problem of laboratory technics, considerable interest should be shown in the program that has been established at Tufts.

The editor of the American Journal of Dental Science estimates the amount of gold foil used in the United States for filling teeth at 6,600 ounces annually — worth about $198,000.

Boston M. & S. J., *January 22, 1851*

OBITUARY

JOHN W. BARTOL

1864–1950

Dr. John Washburn Bartol, a prominent Boston physician for more than half a century, died on Wednesday, November 15, 1950, at his home, 1 Chestnut Street, Beacon Hill, at the age of eighty-six. He had served as president of the Massachusetts Medical Society, the English Speaking Union, the Boston Medical Library and the Boston Health League, and as chairman of the Board of Simmons College.

He was born in Lancaster, Massachusetts, where his father, the Rev. George M. Bartol, was minister of the Lancaster Unitarian church for fifty-nine years. Dr. Bartol graduated from Exeter Academy, from Harvard College in 1887 and from Harvard Medical School in 1891. After an internship at the Boston City Hospital, he studied at Vienna, and began practicing in Boston in 1894. For many years he served as a visiting physician at the Boston City Hospital and over the same period was instructor in clinical medicine at Harvard Medical School. He was a member of the Massachusetts State Board of Health from 1902 until 1907. He was an excellent clinical man and an able convincing teacher. In his relations with patients he was a kindly and reassuring physician, embodying to the highest degree the art of the care of the patient. It was a delight to make ward rounds with him, and his bedside teaching was unforgettable. To his house officers he was an inspiration in thoroughness and kindly human relations.

During World War I, he served in the Army from 1921 until 1923 and rose from the rank of lieutenant to that of major. He was president of the Massachusetts Medical Society from 1921 to 1923 and of the Boston Medical Library from 1927 until 1933.

In 1906, Dr. Bartol was appointed a member of the Corporation of Simmons College, a position that he held at the time of his death. He was a member of the Harvard Club of Boston, The Country Club, and the Dorchester Medical Club.

He leaves his wife, two sons, Dr. George M. Bartol and Louis C. Bartol, of Milton; 4 daughters, Mrs. C. A. Belash and Miss Dorothy Bartol, of Boston, Mrs. Peter Sutcliffe, of South Devon, England, and Mrs. Frederick Grace, of Cambridge; a brother, Dr. Edward F. Bartol, of Lancaster; and 16 grandchildren.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

PERLEY — Melba S. Perley, M.D., of Laconia, died on October 27. She was in her forty-ninth year.

Dr. Perley received her degree from University of Pittsburgh School of Medicine. She was a member of the Radiological Society of North America, American Roentgen Ray Society and American College of Roentgenology.

Her husband, three sons, her parents and a brother survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The February schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

Orthopedic Clinics	Date	Clinic Consultant
Greenfield	February 1	Charles L. Sturdevant
Lowell	February 2	Albert H. Brewster
Salem	February 5	Paul W. Hugenberger
Haverhill	February 7	William T. Green
Brockton	February 8	George W. Van Gorder
Lynn*	February 12	Daniel M. Killoran John J. Crowley
Gardner	February 13	Carter R. Rowe
Hyannis	February 15	Paul L. Norton
Worcester	February 16	John W. O'Meara
Springfield	February 20	Garry deN. Hough, Jr.
Pittsfield	February 21	Frank A. Siowick
Fall River	February 26	David S. Grice

Rheumatic Fever Clinics	Dates
North Reading	February 6, 13, 20, 27
Fitchburg	February 7, 14, 21, 28

Plastic Clinics	Consultant
Eastern Massachusetts Semi-monthly	Bradford Cannon
Western Massachusetts Monthly	Joseph M. Baker

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic will serve Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Hospital.

SURVEY OF RADIOISOTOPE USERS IN MASSACHUSETTS

The recent increase in the use of radioisotopes has prompted the Massachusetts Department of Public Health (Division of Sanitary Engineering) and the Massachusetts Department of Labor and Industries (Division of Occupational Hygiene) to co-operate in a fact-finding survey on the need for regulation of radioisotope users in the State.

A survey form was drawn up covering the following phases of radioisotope use: personnel, medical care in overexposure, radioisotopes used, laboratory design and equipment, waste disposal, instrumentation and hazard monitoring. The list of known users in the State, all of which were covered by the survey, included colleges and universities, hospitals, industrial plants and affiliates, and biologic laboratories.

SURVEY FINDINGS

The survey indicated that the majority of radioisotopes handled in Massachusetts are used in tracer quantities and that the ones most extensively employed are carbon (C^{14}), phosphorus (P^{32}) and iodine (I^{131}).

The investigators also found that there are no generally accepted policies on pre-employment physical examinations, periodic checkups of personnel, regular blood counts or treatment of personnel overexposed to radiation.

Moreover, the survey revealed a need for accepted standards of laboratory design or equipment for the use of radioisotopes; at present, all types of laboratories are found. In general, most installations had monitoring equipment in the form of a beta-gamma survey meter, but personnel protection methods were inadequate except in larger installations that maintained monitoring groups (or health-physics groups).

Finally, greater supervision is needed in the disposal of radioactive materials, because some of the practices are dangerous and are setting precedents that will be hard to eliminate in the future.

The handling of radioisotopes in the State is generally good at present. Instances of carelessness because of indifference or lack of knowledge occur mostly in smaller installations where there are no health-physics groups to check on their practices.

RECOMMENDATIONS

On the basis of their survey, the investigators recommend a pre-employment indoctrination course in radiation for all personnel handling radioisotopes; physical examinations and blood counts before employment and blood counts every three months during employment; a general policy for the prevention of overexposure to or ingestion of radioactive materials; health-physics or monitoring groups to check every laboratory and its personnel for radiation hazards; and a central agency in the State to advise on proper laboratory design and equipment and on proper disposal of radioactive wastes and to see that this advice is carried out.

CORRESPONDENCE

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

To the Editor: At a special meeting of the American Board of Obstetrics and Gynecology, held in Pittsburgh, Pennsylvania, December 14, 1950, the following changes in the regulations of the Board were unanimously adopted:

That physicians otherwise qualified, who were graduated before January 1, 1939 and whose required training was

in obstetrics or gynecology alone, and who have confined their practice to obstetrics or gynecology for at least five (5) years immediately prior to application be accepted for examination as candidates for certification in either obstetrics or gynecology. In all other respects requirements for eligibility remain the same for those physicians graduated since 1939. Bilateral training is required as published in the Bulletin of the Board.

Applicants who have been certified by one of the other American specialty examining boards will not be eligible for certification by this Board until they have relinquished the certificate previously conferred.

Since the vast majority of obstetrical and gynecological cases are nonoperative the Board requires adequate training in basic sciences, infertility, endocrinology, oncology, irradiation therapy, psychosomatic medicine, electrotherapy, and other nonoperative methods of diagnosis and treatment as well as training in major operative procedures.

PAUL TITUS, M.D.
Secretary

Pittsburgh, Pennsylvania

NOTICES

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The Boston City Hospital House Officers' Association will present the following lectures, to be given in the Dowling Amphitheater at 7 p.m., in its evening lecture series.

January 30. Present Status of the Etiology and Clinical Diagnosis of Cancer of the Lung. Ernest Wynder, M.D., of Georgetown University Medical Center, Washington, D. C.

February 6. Host Factors in Poliomyelitis. Louis Weinstein, M.D., associate professor of medicine, Boston University School of Medicine, chief of Infectious Disease Service, Massachusetts Memorial Hospitals and lecturer in medicine, Harvard Medical School. Discusser: Dr. Conrad Wesselhoeft.

All interested persons are invited to attend.

MASSACHUSETTS SOCIETY OF ANESTHESIOLOGISTS

The fourth session of the annual postgraduate education course of the Massachusetts Society of Anesthesiologists will be held in the Bigelow Amphitheater of the Massachusetts General Hospital, Boston, on February 3, from 2:30 to 5:00 p.m. The subject of the course will be "Pulmonary Pathology Relative to the Resuscitation of the Newborn: Diagnostic Features from the Pathological, Radiological, and Clinical Viewpoints." The speakers will be Dr. H. Edward MacMahon, professor of pathology, Tufts College Medical School and chief pathologist, New England Center Hospital, and Dr. Charles Bernstein, associate radiologist, New England Center Hospital.

Dr. Benjamin Etsten, director of anesthesiology, New England Center Hospital, will be chairman.

AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS

The sixty-second annual meeting of the American Association of Genito-Urinary Surgeons will be held at Skytop Lodge, Skytop, Pennsylvania, May 16, 17 and 18, 1951.

Names of candidates for membership should be in the hands of the secretary by February 10, 1951, in order that they may be published and distributed to the members of the Association for their consideration one month before the meeting.

A candidate's proposal should include a letter from the proposer, one from the seconder, and such other letters of recommendation as may be submitted, together with a statement of the candidate's academic and medical degrees and hospital and teaching positions, and a list of his medical publications.

Titles of papers should be sent to the secretary as soon as possible. Contributions to the program will be accepted up to February 25, unless the program is filled before that time.

AEC FELLOWSHIPS IN INDUSTRIAL MEDICINE

The United States Atomic Energy Commission will offer four fellowships in industrial medicine for the 1951-52 academic year, continuing a special fellowship program begun last September. The program is administered for the AEC by the Atomic Energy Project of the School of Medicine and Dentistry, University of Rochester, Rochester, New York, and fellows are selected by a committee headed by Dr. James H. Sterner, Associate Medical Director of the Eastman Kodak Co. and Consultant in Industrial Health to the AEC.

Applications for the fellowships should be submitted by March 1, 1951, to:

A. E. C. Fellowships in Industrial Medicine, Atomic Energy Project, School of Medicine and Dentistry, University of Rochester, Rochester, New York.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 29. Suffolk District Medical Society. Page 37, issue of January 4.
JANUARY 30. Boston City Hospital House Officers' Association. Notice above.
JANUARY 31. American Academy of Orthopaedic Surgery (see Kappa Delta Award for Research in Orthopedic Surgery). Page 736, issue of May 4.
FEBRUARY 3. Massachusetts Society of Anesthesiologists. Notice above.
FEBRUARY 6. Boston City Hospital House Officers' Association. Notice above.
FEBRUARY 8. Leukemia. Dr. Joseph Ross. Pentucket Association of Physicians. 8:30 p.m. Haverhill.
FEBRUARY 9. Beta Iota Chapter of Nu Sigma Nu. Page 1018, issue of December 21.
FEBRUARY 9. Cutter Lecture. Page 116, issue of January 18.
FEBRUARY 11. National Conference on Medical Services. Page 38, issue of January 4.
FEBRUARY 12-14. American College of Allergists. Page 74, issue of January 11.
FEBRUARY 13. New England Society of Anesthesiologists. Page 512, issue of September 28.
FEBRUARY 21. Bay State Society for the Crippled and Handicapped. Page 1066, issue of December 28.
FEBRUARY 27. Norfolk District Medical Society. Page 629, issue of October 19.
MARCH 5-8. New Orleans Graduate Medical Assembly. Page 1018, issue of December 21.
MARCH 7. Hampshire District Medical Society. Page 170, issue of July 27.
MARCH 11-16. College of Medical Evangelists. Page 74, issue of January 11.
MARCH 22. Hyman Morrison Lecture. Page 74, issue of January 11.
MARCH 26. Boston Lying-in Hospital Obstetric Round-Table Conference. Page 629, issue of October 19.
MARCH 27. Norfolk District Medical Society. Page 629, issue of October 19.
APRIL 9-13. American College of Physicians. Page 296, issue of June 15.
APRIL 10. New England Society of Anesthesiologists. Page 512, issue of September 28.
APRIL 24. Norfolk District Medical Society. Page 629, issue of October 19.
MAY 8. New England Society of Anesthesiologists. Page 512, issue of September 28.
MAY 9. Norfolk District Medical Society. Page 629, issue of October 19.
MAY 16. New England Obstetrical and Gynecological Society. Hillcrest Country Club, Leicester, Massachusetts.
MAY 16-18. American Association of Genito-Urinary Surgeons. Notice above.
MAY 22-24. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.
MAY 24-26. American Goiter Association. Columbus, Ohio.
SEPTEMBER 19. American Medical Writers' Association. Page 1066, issue of December 28.
SEPTEMBER 19-21. Mississippi Valley Medical Society. Page 1066, issue of December 28.
OCTOBER 31. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.
NOVEMBER 10-21. Pan-Pacific Surgical Association. Page 680, issue of October 26.
JULY 8-11, 1952. Thirteenth British Congress of Obstetrics and Gynaecology. Page xv, issue of December 14.

DISTRICT MEDICAL SOCIETIES

HAMPSHIRE

MARCH 7. 4:30 p.m. Cooley-Dickinson Hospital, Northampton.
MAY 2. 4:30 p.m. Annual Meeting. Jones Library, Amherst.

(*Notices concluded on page xv*)